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THE DISAPPEARANCE OF INTRAVENOUSLY INJECTED LYMPHOCYTES IN THE ABSENCE OF THE GASTRO-INTESTINAL TRACT.

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It is generally concluded that old or worn-out and transfused erythrocytes may leave the circulating blood by either of two mechanisms; phagocytosis by the reticulo-endothelial system[2,3,18] or cellular fragmentation and subsequent lysis.[19,20,25] Granulocytes and monocytes also may be removed by these mechanisms. But, beside phagocytosis and autolysis[5,8,15,17] two additional explanations for the disappearance of lymphocytes have been suggested, viz., differentiation into red blood cells[11,12] and excretion into the lumen of the gastro-intestinal tract.[1,10,24] The present study reveals that the gastro-intestinal tract plays only a minor rôle, if any, in the elimination of lymphocytes from the general circulation.

Methods and Materials. New Zealand Red rabbits, which weighed approximately 1500 gm. each, were used. All blood determinations were made by the use of standardized techniques and equipment. Sodium amytal, the administration of which is followed by a peripheral leukopenia[9] (Table 1), but only a mild lymphopenia, was selected as the anesthetic of choice.

Viable lymphocytes were obtained by removing and suspending, in saline, the cells of the submucosa of rabbit appendices which were secured surgically. Triple washing in saline was necessary to remove tissue fibrinogen. Five per cent of the cells were monocytes and clasmatocytes and 95% were lymphocytes (50%–60% young, 30%–40% mature, and 10% old forms—Wiseman criteria[26b]). The total number of lymphocytes varied from 100 million to 3 billion in different appendices.

Gastro-enterectomy was performed through a large midline abdominal incision by the double ligation and severance of the rectum, inferior and superior mesenteric vessels, celiac axis, esophagus and portal vessels which permitted the removal of the stomach, spleen, pancreas, mesenteric lymph nodes, duodenum, small intestines, colon and sigmoid in one mass. The

kidneys remained intact. As soon as the effects of the anesthesia wear off, gastro-enterectomized rabbits jump and hop about quite normally and will live from 8 to occasionally 24 hours.

TABLE 1.—EFFECT OF AMYTAL ON LEUKOCYTE COUNT.

The total leukocyte counts (expressed in hundreds per c.mm.) of 6 rabbits made before and after the intravenous injection of 50 mg. of sodium amytal per kilo of body weight are listed below. In 5 rabbits the anesthetic was administered on 4 occasions, each administration 24 hours apart. Hemoglobin estimations also were made but no significant changes occurred.

Rabbit No.	Anesthesia.	Pre-injection.	15 min. post-inj.	30 min. post-inj.	1 hr. post-inj.	2 hrs. post-inj.
27	First	92	78	86	45	39
	Second	87	..	86	50	60
	Third	101	..	50	58	45
	Fourth	96	54	46	65	80
28	First	71	..	44	50	58
	Second	82	..	62	68	72
	Third	94	82	..	62	61
	Fourth	88	..	81	60	70
29	First	74	61	46	81	121
	Second	92	..	50	78	92
	Third	89	71	39	41	78
	Fourth	99	78	82	72	112
30	First	81	..	33	50	66
	Second	82	..	52	70	69
	Third	53	54	41	35	91
	Fourth	74	40	86	90	
26	First	75	52	40	51	72
	Second	90	..	44	52	76
	Third	66	..	50	..	91
	Fourth	78	..	45	80	90
14	First	94	80	60	68	102
Averages		83.2	65.8	61.1	65.3	77.2

Experiments and Results. *Experiment 1* (*Table 1*). Five normal rabbits were injected intravenously with sodium amytal (50 mg. per kilo) every day for 4 days, inducing a deep anesthesia of approximately 2 hours' duration. An additional rabbit was given a single injection. Total leukocyte counts and hemoglobin estimations were made before, 15 and 30 minutes, 1 and 2 hours, after the administration of the drug. There were no significant changes in the estimations of hemoglobin and the depression of the leukocyte levels following anesthesia was slight and of about 2 hours' duration. No change of a permanent character was noted in the numbers of circulating white blood cells during the 4-day period. In fact, in most instances the leukopenia after the fourth induction of anesthesia was less severe than that after the first.

Experiment 2 (*Table 2 and Chart 1*). Table 2 illustrates the recorded estimation of the blood levels before and after amytalization, splenectomy and gastro-enterectomy of 5 litter mates. Each procedure was separated by a period of 24 hours. In 2 rabbits (Nos. 46 and 50) there was a decrease of, in one (No. 49) there was an elevation of, and in 2 (Nos. 51 and 55) no change of the absolute numbers of lymphocytes, 5 hours after the induction of the anesthesia. Five hours after splenectomy the levels of the blood of each rabbit had returned essentially to those noted preoperatively. But 5 hours after gastro-enterectomy a severe lymphopenia became evident, and the low level persisted until death in spite of the fact that 3 of the 4 rabbits developed a leukocytosis.

TABLE 2.—LYMPHOCYTES AFTER AMYTALIZATION, SPLENECTOMY AND GASTRO-ENTERECTOMY.

The absolute numbers of lymphocytes, the percentages of lymphocytes and the total number of white blood cells (expressed in hundreds per c.mm.) of 5 rabbits which were first amytalized, and after a 24-hr. period were amytalized and splenectomized, and finally after a second 24-hr. period 4 were amytalized and gastro-enterectomized. Hemoglobin estimations were made simultaneously with each differential, but the changes were insignificant.

		Amytal (50 mg. per kilo).					←24 hrs.→Amytal and splenectomy.←24 hrs.→				Amytal and gastro-enterectomy.					
Rabbit.	Lymphocytes and W. B. C.	Pre-anes-thesia.	30 min. post-anes-thesia.	1 hr.	3 hrs.	5 hrs.	Pre-anes-thesia.	1 hr. post-anes-thesia.	3 hrs.	5 hrs.	Pre-anes-thesia.	1 hr. post-anes-thesia.	4 hrs.	6 hrs.	8 hrs.	15–19 hrs.
46	Absolute No.	20	20	9	8	11	11	9	17	9	14	5	2	2	3	3
	Per cent	28	29	32	10	16	21	28	25	13	20	20	5	5	3	8
	Total W. B. C.	68	70	29	83	68	57	30	74	80	73	24	42	40	92	40
50	Absolute No.	24	20	..	12	10	28	22	18	25	30	7	3	4	3	4
	Per cent	30	37	..	13	13	40	45	26	25	30	20	3	4	5	5
	Total W. B. C.	80	56	..	112	80	70	51	68	103	114	34	116	102	68	170
51	Absolute No.	24	10	19	..	20	12	7	10	12	10	8	3	3	3	4
	Per cent	32	26	30	..	33	20	22	24	24	13	14	5	10	5	3
	Total W. B. C.	86	38	64	..	65	64	34	44	54	80	57	66	31	75	146
55	Absolute No.	14	..	16	17	13	22	18	..	18	16	12	7	3	4	4
	Per cent	18	..	28	25	21	29	29	..	20	20	23	13	6	6	3
	Total W. B. C.	68	..	56	68	63	74	60	..	91	80	53	55	62	67	152
49	Absolute No.	10	13	22	..	19	12	9	..	18						
	Per cent	21	44	19	..	20	19	15	..	21						
	Total W. B. C.	54	32	112	..	96	66	59	..	94						
Averages:																
	Absolute No.	18	16	14	..	14	17	16	..	17	17	8	3	3	3	3
	Per cent	28	39	27	..	21	26	28	..	19	20	19	6	6	5	4
	Total W. B. C.	71	49	65	..	74	66	51	..	92	86	42	69	57	75	127

Chart 1 illustrates the persistent lymphopenia which followed the gastro-enterectomy of 8 additional rabbits. Six of the 8 developed a terminal leukocytosis.

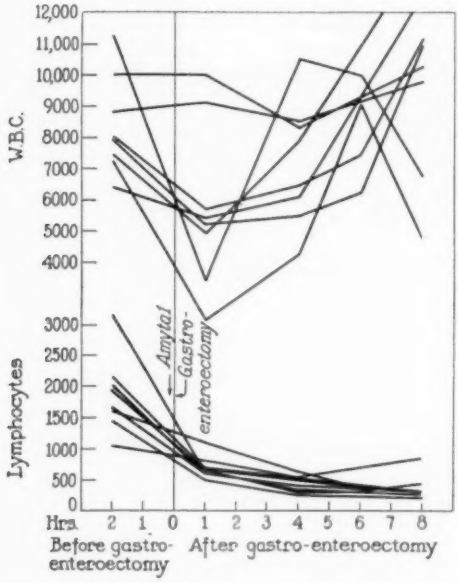

CHART 1.—The number of leukocytes (per c.mm.) and the absolute numbers of lymphocytes (per c.mm.) in the peripheral circulation of 8 rabbits before and after gastro-enterectomy.

Experiment 3 (*Table 3*). In 2 gastro-enterectomized rabbits (Nos. 43 and 44) the peripheral lymph nodes, viz., the axillary, inguinal and popliteal, were removed. By examining Table 3, it can be observed that there was no essential difference in blood levels of these rabbits and those of Experiment 2. And it may be assumed that the peripheral lymph nodes produced few circulating lymphocytes.

TABLE 3.—EFFECT OF GASTRO-ENTERECTOMY AND LYMPHADENECTOMY ON LYMPHOCYTE LEVELS.

The table illustrates the absolute numbers and percentages of lymphocytes, the total numbers of white blood cells (expressed in hundreds per c.mm.) and the percentage of hemoglobin, at preoperative and postoperative intervals, of 2 rabbits from which the stomach, small and large intestines, spleen and mesenteric, popliteal, inguinal and axillary lymph nodes had been removed.

Rabbit No.	Lymphocytes, W. B. C. and hemoglobin.	Preop.	1 hr. postop.	4 hrs. postop.	6 hrs. postop.	8 hrs. postop.	9 hrs. postop.
43	Absolute No.	30	11	9	..	0.6	
	Per cent	60	50	16	..	2	
	Total W. B. C.	50	23	55	..	36	
	Hemoglobin (%)	94	96	84	..	92	
44	Absolute No.	10	10	6	2	1	2
	Per cent	20	28	11	3	4	5
	Total W. B. C.	52	38	63	70	4)	40
	Hemoglobin (%)	100	91	83	94	91	104

Experiment 4 (*Chart 2*). This experiment was performed to demonstrate the changes in the number of circulating leukocytes and lymphocytes of normal rabbits which received intravenous injections of heterogenetic lymphocytes. Normal rabbits weighing 1500 gm. contain about 100 cc. of blood, and intravenous injections of normal lymphocytes should raise the total number of circulating white blood cells correspondingly.

As is illustrated, Rabbit 65 was given intravenously 192 million lymphocytes suspended in 10 cc. of saline, and Rabbit 66, 332 million (Chart 2). The total number of leukocytes decreased immediately after the injections in both animals, and a return to the former normal levels did not occur until after a period of 2 to 3 hours had elapsed. There was a slight but temporary elevation in the number of circulating lymphocytes, followed by a compensatory depression and then a gradual return to the original normal levels all within 6 hours. It is apparent therefore that only a relative lymphocytosis existed very temporarily after the introduction of viable lymphocytes into these normal rabbits.

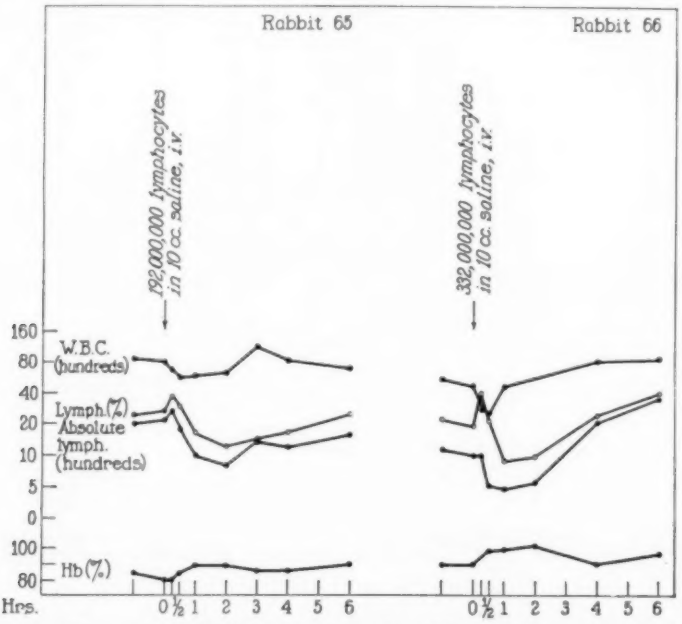

CHART 2.—Changes in the leukocyte, lymphocyte and hemoglobin levels of 2 rabbits after the intravenous administration of viable lymphocytes.

In no respect did these animals develop abnormal reactions to the injection.

Experiment 5 (*Charts 3–6*). If the gastro-intestinal tract is the site of lymphocyte excretion, the intravenous injection of lymphocytes into the circulating blood of rabbits, from which the gastro-intestinal tract has been removed, should be followed by an elevation, and a maintenance of the elevation, of the number of these circulating cells. The results of the experiment are described in four parts.

Chart 3. Blood examinations were made before and at irregular intervals after gastro-enterectomy until death of Rabbit 59. As illustrated, the percentage and absolute number of lymphocytes declined sharply after

gastro-enterectomy. Three and one-half hours after the operation the percentage of lymphocytes was 7 and the absolute number 400. At this time 10 million autogenetic lymphocytes which had been suspended in 10 cc. of saline were given intravenously. The injection was followed by no significant change in the levels of the blood cells. One hour and 45 minutes later, long after any influence that the first injection may have had on the lymphocyte level, 2 billion 600 million heterogenetic lymphocytes suspended in 10 cc. of saline were administered intravenously. Fifteen minutes after this injection the percentage of lymphocytes increased to 17.5 and the absolute number to 700. However, within 3½ hours the percentage had returned to the former level of 5 and the absolute number to 400. At

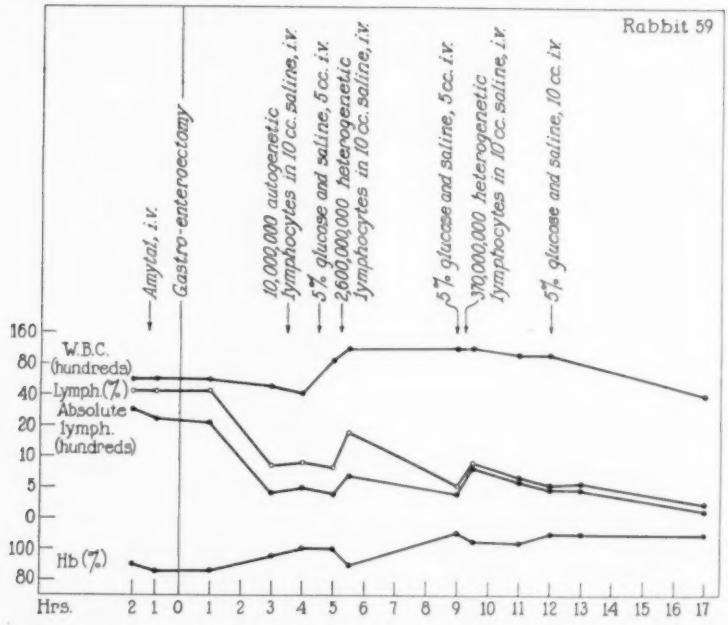

CHART 3.—Changes in the lymphocyte, leukocyte and hemoglobin levels of Rabbit 59 after gastro-enterectomy and after the intravenous administration of viable lymphocytes.

that time, a third injection of 370 million heterogenetic lymphocytes was given intravenously. The elevation in the numbers of circulating lymphocytes following the injection was slight and insignificant. The animal died 17 hours after gastro-enterectomy with the total leukocyte level within the normal range but with a severe lymphopenia—the absolute number being 150. In this gastro-enterectomized animal, intravenously administered autogenetic and heterogenetic lymphocytes disappeared rapidly from the blood stream.

The behavior of the animal was not unusual at any time. After the effects of the anesthetic had worn off the animal jumped and hopped about normally until after the third injection of cells. A prone position was then assumed. The rabbit did not lose its sense of balance until 1 hour before death.

The body temperature was maintained at a normal level by the use of electric lamps.

Chart 4 illustrates the findings of Rabbit 62. The leukocyte and lymphocyte levels were followed before and after administration of amytal, splenectomy and gastro-enterectomy. One and a half hours after the latter operation 2 billion, 230 million autogenetic lymphocytes were administered intravenously. The leukocyte count before was 10,500, but 15 minutes after the injection was 1550. The percentage of lymphocytes increased from 6.5% before to 25% after and the absolute number from 550 to 1000. Within 2 hours the levels approximated those present immediately previous to injection. Just before death, 11 hours after gastro-enterectomy, leukocyte count was 6000; the percentage of lymphocytes was 7.5 and the absolute number was 500.

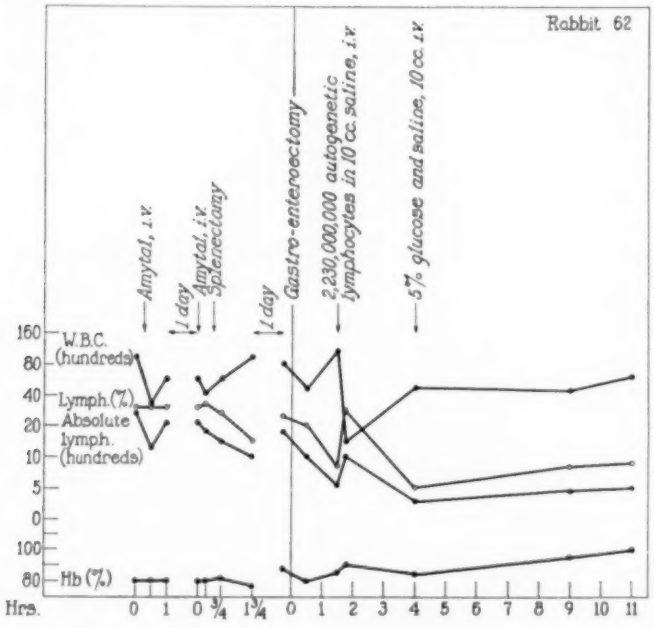

CHART 4.—Changes that occurred in the leukocyte, lymphocyte and hemoglobin levels of Rabbit 62 after each of the following: anesthesia, splenectomy, gastro-enterectomy and the intravenous injection of viable autogenetic lymphocytes.

The gradual elevation of the percentage of hemoglobin previous to death might well be a result of dehydration because urine was excreted in large quantities during the entire experiment.

The behavior of this animal was similar to that of the first rabbit.

Chart 5 illustrates the hematologic findings of Rabbit 64, which was first amytalized, 24 hours later splenectomized and then after another interval of 24 hours was gastro-enterectomized. Following the latter operation, the decline of the number of circulating lymphocytes was gradual and of a permanent nature. After an injection of 201 million autogenetic lymphocytes, the rate of the decline was temporarily decreased. But by the third hour after injection the absolute number of lymphocytes had decreased to the low level of 400. This level was maintained until death, 15 hours later.

The hemoglobin level did not vary significantly during the period from splenectomy until death.

Chart 6 illustrates the changes of the leukocyte and lymphocyte levels of Rabbit 61, to which lymphocytes were administered both before and after gastro-enterectomy. The intact animal was given intravenously 168 million heterogenetic lymphocytes. An increase occurred in the number of leukocytes from 7100 before to 9500 three hours after the injection, but the percentage of lymphocytes declined from 24 to 10, and the absolute number from 1650 to 950. Two days later the percentage of

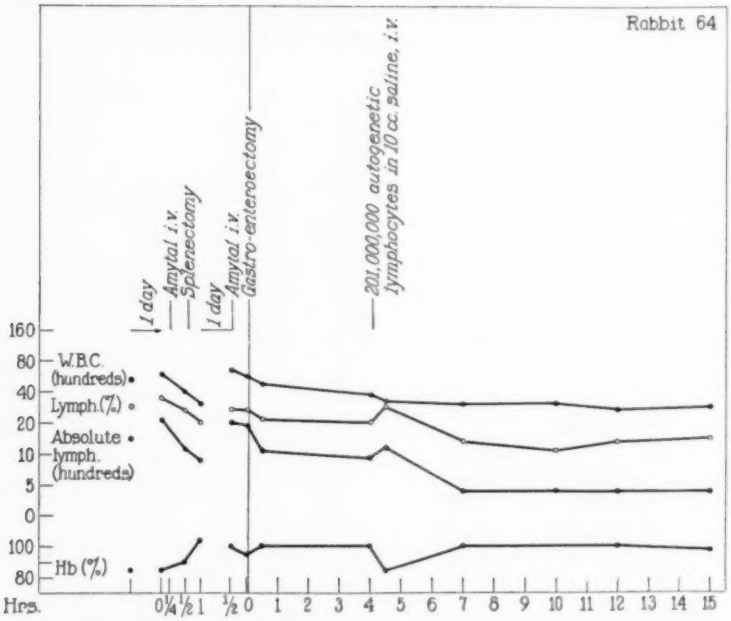

CHART 5.—Changes in the leukocyte, lymphocyte and hemoglobin levels of Rabbit 64 after each of the following: splenectomy, gastro-enterectomy and the intravenous injection of viable autogenetic lymphocytes.

lymphocytes rose to 40% and the absolute number to 2000. Immediately following splenectomy the anticipated temporary decline in the number of leukocytes and lymphocytes occurred. Twenty-four hours later the levels, however, were essentially the same as those present at the time of the injection of lymphocytes, 72 hours earlier. Gastro-enterectomy was then performed, and the usual lymphopenia developed. Three hours after the operation 200 million autogenetic lymphocytes were administered intravenously. There was a sharp rise in the percentage and absolute number of lymphocytes following the injection. The percentage before was 15 but 15 minutes after the injection 34; the absolute number before was 550, and after, 800. However, the leukocyte level remained very constant at about 3500 during the 2-hour period, but later it increased gradually and reached a peak of 14,000 at the time of death 17 hours after gastro-enterectomy and 14 hours after the second injection of lymphocytes. During the last 12 hours of the rabbit's life, the absolute number of lymphocytes remained below 500. This rabbit destroyed intravenously administered lymphocytes as rapidly after the removal of the intestines as before.

The essential postmortem findings of the 4 rabbits used in Experiment 5 were: diffuse congestion of the lungs, edema of the myocardium, toxic nephritis, acute degenerative hepatitis, normally hyperplastic bone marrow and small hemorrhages in the cervical and axillary lymph nodes. The popliteal nodes were hypoplastic. No accumulation of lymphocytes was observed in any of the tissues examined.

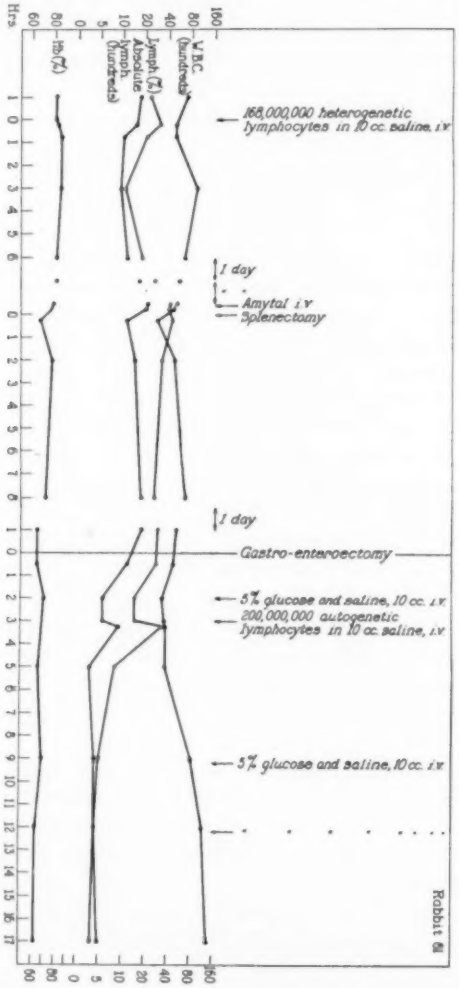

CHART 6.—Changes in the leukocyte, lymphocyte and hemoglobin levels of Rabbit 61 after each of the following: intravenous injection of heterogenetic lymphocytes before surgical alterations, splenectomy, gastro-enterectomy and the intravenous administration of autogenetic lymphocytes after gastro-enterectomy.

Discussion. The mechanisms responsible for the destruction of normal tissue and blood cells, which are constantly being replaced, are poorly understood. It is apparent that the process of lysis is an

important factor in the destruction of malignant cells in susceptible animals made immune to experimental cancer[7,15] and leukemia.[16] The results of the experiments presented above are not in opposition to similar suppositions in relation to normal cells.

The evidence that severe and persistent lymphopenia occurs immediately following gastro-enterectomy favors the hypothesis that many if not the majority of circulating lymphocytes reach the blood stream from some portion of the gastro-intestinal tract, presumably the lymphoid tissue of the submucosal layer. (Drugs,[23] infections, irradiations, bodily temperature changes,[26a] emotions,[6] anesthesia[9,27b] and normal rhythmicity[21] may occasionally be responsible for decreases in the absolute number of circulating lymphocytes.) The fact that tremendous numbers of lymphocytes are present in the lymph of the thoracic duct of man and animals has led many observers[1,13,14,26a,27a,28] previously to draw this conclusion. Yoffey and Drinker[28,4] state that one out of every 30 lymphocytes entering the blood stream comes from the tissue spaces, which may well explain the presence of the lymphocytes that persisted until death of the animals described herein. In 2 chickens Scott and Cook[22] noted a selective decrease in the number of circulating lymphocytes following large feedings of radioactive phosphorus. After the deposition of the radio-phosphorus in the bones, it became selectively destructive to the myeloid cells. Such selectivity ultimately may be important in the therapy of leukemia.

With the exception of leukemia (if leukemia is a neoplasm) neoplastic metastases rarely occur in the submucosa of the gastro-intestinal tract, a fact that the proponents of the theory that lymphocytes are the defense agents against cancer do not emphasize.

The results of the above experiments also provide evidence that not all of the lymphocytes are discarded through the gastro-intestinal mucosa. The fate of the huge numbers of lymphocytes that were injected into the animals is unknown, but they were not excreted through intestinal mucosa and they were not phagocytized by the reticulo-endothelial system since the majority of both were removed. And the reticulum cells of the bone marrow, examined microscopically, were not actively phagocytic. Presumably lysis played a predominant rôle.

Conclusions. 1. Many circulating lymphocytes in rabbits take origin from some portion of the gastro-intestinal tract, presumably the submucosal lymphoid layer.

2. A severe and persistent lymphopenia occurred within 2 hours following the removal of the stomach and intestines of 18 rabbits.

3. Viable lymphocytes, either autogenetic or heterogenetic administered intravenously to either normal or gastro-enterectomized rabbits disappear very rapidly from the circulating blood.

4. Excretion of lymphocytes through the mucosa of the stomach and intestines is not the only mechanism responsible for lymphocyte destruction.

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THE ANTIANEMIC PRINCIPLE IN THE HUMAN LIVER IN CARCINOMAS OF THE STOMACH AND CECUM.

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The relationship between gastric secretion and hematopoiesis was first established by Castle.[2] Sturgis and Isaacs[12] and Sharp,[11] by their successful treatment of pernicious anemia with desiccated whole hog stomach, added further evidence that this organ produces an active hematopoietic principle. Castle,[3] on the basis of a long series of experiments performed by himself and his associates, concluded that an "intrinsic factor" present in the normal gastric juice interacts with an "extrinsic factor" present in food to produce an antianemic principle. Although there is general agreement that this principle is formed by the stomach and stored in the liver, considerable controversy has arisen concerning its production and nature.[6,10]

Bence,[1] like Goodman and his associates,[5] found that after total gastrectomy the antianemic principle of hog's liver was depleted. Henning and Brugsch[7] observed that the most active antianemic effect is obtained from the mucosa of the pyloric antrum and their observation was confirmed by Meulengracht,[9] who advanced the opinion that Brunner's glands in the submucosa of the duodenum might also be the source of the antianemic principle.

Goldhamer[4] demonstrated the absence of the "intrinsic factor" in the gastric juice of a patient who had a macrocytic anemia and who was shown by roentgenologic examination to have a scirrhous carcinoma of the stomach. Ventriculin was used as a control therapy. In view of this observation it was of interest to test the antianemic potency of the livers of patients with carcinomas which had destroyed various portions of the gastro-intestinal tract.

Materials and Methods—Tests were made of the antianemic potency of extracts prepared from the livers of 2 patients who died of carcinoma of the stomach and from the liver of a third patient who died of carcinoma of the cecum. In the first case of gastric carcinoma the neoplasm involved all of the pyloric and prepyloric regions; in the second case, all of the stomach except a portion of the pars pylorica was involved. The potency of the extract of the liver of a markedly anemic and emaciated patient with carcinoma of the cecum was tested to ascertain whether the hepatic antianemic principle would be depleted in a subject with an intestinal neoplasm but no gastric lesion. As control therapy either commercial liver extract (Lilly) was used, or an extract prepared from the liver of a patient who died of cerebral hemorrhage but whose gastro-intestinal tract was normal.

The postmortem examinations were performed between 1 and 2 hours after death. The livers thus secured were kept in an electric refrigerator at a temperature of 4° C. for periods varying from 48 to 120 hours before the extracts were manufactured, and the liver from which the control extract was made was kept in the refrigerator for the same period of time.

The liver extracts were made according to the Lilly method (Sol. Liver Extr.—Lilly, N.N.R., 1937, p. 320) as follows:

After the livers had been thoroughly ground in a meat grinder, approximately 4 times their weight in distilled water was added to them. The reaction, with the aid of a glass electrode, was adjusted to a pH of between 5 and 6 by the addition of a sufficient amount of concentrated HCl. The mixture was heated to approximately 80° C., stirred at that temperature for 30 minutes, and filtered. After the precipitated proteins had been allowed to settle, the supernatant fluid was decanted and was filtered through a fast filter paper, onto which the residue was finally poured. The clear filtrate was reduced in a vacuum to a small volume (200 to 500 cc.) and sufficient alcohol was added to bring the concentration to 70% of alcohol. The solution was placed in the refrigerator overnight (at 4° C.) and the resulting precipitate was separated by filtration and discarded. The filtrate was reduced to a syrupy consistency by vacuum distillation and the residual solution was then added to 25 volumes of 95% alcohol. The solution was again placed in the refrigerator overnight and the precipitated material was recovered by decantation and subsequent centrifugalization of the residue. The precipitated material was dissolved in physiological saline (Experiment 1) and in an aqueous 1 to 10,000 merthiolate solution (Experiments 2 to 4), 1 cc. of solvent being used for each 9 to 15 gm. of the original liver. The resulting solution of liver extract was

centrifugalized at about 3300 revolutions per minute and then sterilized by filtration through a Seitz filter. After filtrations the extracts were cultured and found to be sterile. When they were injected intravenously into anesthetized dogs there were no significant pressor or depressor effects.* When the extracts were stored in the refrigerator before use a fine precipitate appeared, but it readily dissolved at room temperature. This precipitate can be discarded without any material loss of the antianemic principle.[8]

EXPERIMENT 1.—*Extract from the liver of a patient with scirrhous carcinoma of the pyloric and prepyloric regions* (A–38–851). The patient was a colored female of 57, who had complained for 2 years of sore mouth, epigastric pain, vomiting of dark-colored material after meals, and gradual loss of weight. She died of bronchopneumonia shortly after admission to the hospital, before a complete hematologic study could be made. The necropsy, which was performed an hour after death, revealed a scirrhous carcinoma involving the entire pyloric and prepyloric regions of the stomach. Histologic study showed that the mucosa of these regions had been entirely replaced by the neoplastic growth. The mucosa of the remainder of the stomach was normal and there was no evidence of visceral metastasis.

The patient used for the determination of the antianemic principle was a white male of 54 who had a typical Addisonian pernicious anemia in relapse, with nervous symptoms. Hematologic examination revealed 1,740,000 red cells and 4800 white cells per c.mm. The hemoglobin value (Hellige) was 7.8 gm. (56%). The mean corpuscular volume was 132 cu. microns and the mean corpuscular hemoglobin 45 micromicrograms. The percentage of reticulocytes was 1.1. Achlorhydria was persistent following the administration of histamine.

The intramuscular injection in 3 doses of 9 cc. of liver extract (representing 126 gm. of whole liver) failed to produce an increase in the reticulocyte count over a period of 9 days. On the tenth day 9 cc. of the control extract (representing 135 gm. of whole liver) from the patient with cerebral hemorrhage was administered intramuscularly in a single dose. Within 24 hours an elevation occurred in the number of reticulocytes, which reached a peak of 22% on the sixth day following. By the eleventh day the number of red blood cells had increased to 2,650,000 and the hemoglobin value had increased to 11.3 gm. (78%) (Hellige). The total period of observation covered 20 days (Chart 1).

EXPERIMENT 2.—*Extract from the liver of a patient with scirrhous carcinoma of the stomach not involving the pyloric region* (A–39–205). The patient was a markedly emaciated white male of 62 who had complained of gradually increasing epigastric pain and progressive loss of weight over a period of several months. Hematologic examination revealed 4,000,000 red cells and 10,850 white cells per c.mm. The necropsy, which was performed 2 hours after death, revealed a scirrhous carcinoma involving the entire stomach wall except for a circular area 3 cm. in width just proximal to the pyloric ring. The lower 3 cm. of the esophagus was also involved in the neoplastic growth. Two metastatic nodules, each 1 cm. in diameter, were present in the liver and metastasis had occurred to the regional lymph nodes. Peritoneal carcinomatosis was also present. Histologic examination of the grossly uninvolved pyloric area revealed normal mucosa and no evidence of neoplastic tissue. Examination of the remainder of the stomach showed involvement of all coats except for occasional areas in which small amounts of partially atrophic mucosa remained.

The patient used for the determination of the antianemic principle in the liver was a white female of 65 with a macrocytic hyperchromic anemia.

* These tests were kindly performed by Dr. A. G. Eaton of the Department of Physiology.

She had had severe diarrhea. Hematologic examination revealed 1,200,000 red cells and 5000 white cells per c.mm. The hemoglobin value (Hellige) was 4.6 gm. (31%). The mean corpuscular volume was 133 cu. microns and the mean corpuscular hemoglobin 38 micromicrograms. The percentage of reticulocytes was 1. The free hydrochloric acid content of the gastric secretion was 33–60 before the administration of histamine and 42–80 afterward. Bone marrow puncture revealed numerous megaloblasts.

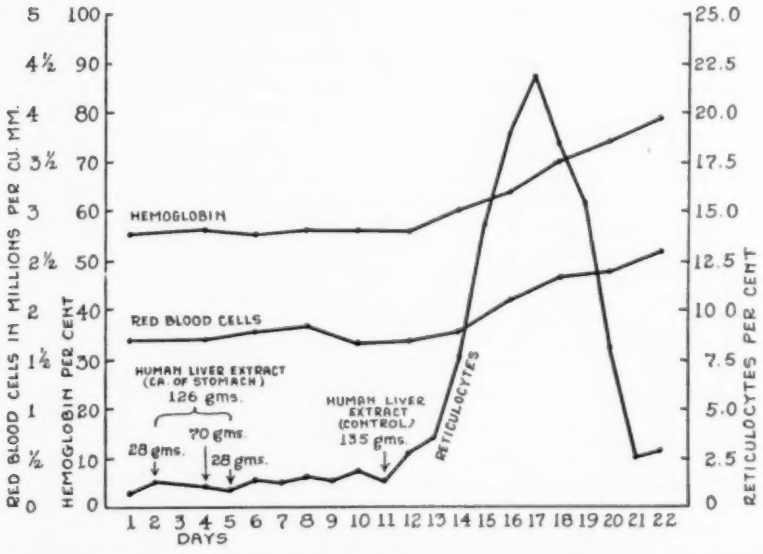

CHART 1.—The failure of response to human liver extract from a case of scirrhous carcinoma of the pyloric and prepyloric portions of the stomach.

The intramuscular injection in a single dose of 12 cc. of liver extract (representing 126 gm. of whole liver) produced a marked reticulocyte response which reached a maximum of 20% on the eighth day following (Chart 2). The patient responded well to subsequent administrations of commercial liver extract.

EXPERIMENT 3.—In order to confirm the observations regarding the content of the antianemic principle of liver extracts prepared in Experiments 1 and 2, another untreated patient with typical Addisonian pernicious anemia in relapse was treated with them. This patient, a white male of 52, had 1,220,000 red blood cells and 5600 white blood cells per c.mm. The hemoglobin value (Hellige) was 5.1 gm. (36%). The mean corpuscular volume was 114 cu. microns and the mean corpuscular hemoglobin 42 micromicrograms. The average percentage of reticulocytes was 0.7. Achlorhydria was persistent following the administration of histamine. Bone marrow puncture revealed numerous megaloblasts.

The intramuscular injection in a single dose of 10 cc. of liver extract (representing 140 gm. of whole liver) from the patient with scirrhous carcinoma of the pylorus (Experiment 1) failed to produce any reticulocytic stimulation during 11 days of observation (Chart 3). The intramuscular injection of 12.5 cc. of liver extract (representing 131.3 gm. of whole liver) from the patient with carcinoma of the stomach which did not involve the pylorus (Experiment 2) produced a significant reticulocyte response within 7 days (Chart 3).

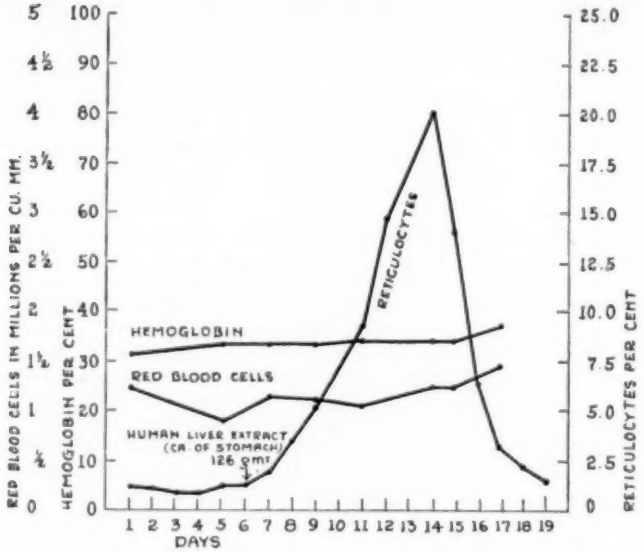

CHART 2.—The response to human liver extract from a case of scirrhous carcinoma of the stomach not involving the pyloric region.

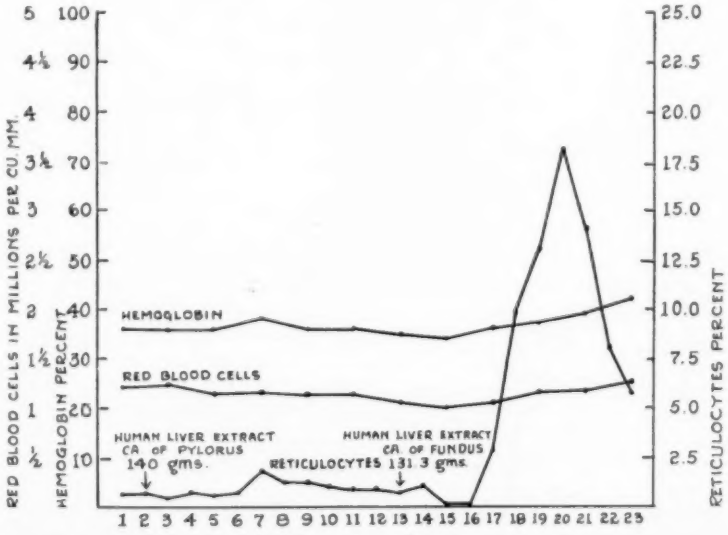
RED BLOOD CELLS IN MILLIONS PER CU. MM.
HEMOGLOBIN PERCENT
RETICULOCYTES PERCENT
HEMOGLOBIN
RED BLOOD CELLS
HUMAN LIVER EXTRACT CA. OF PYLORUS 140 gms.
HUMAN LIVER EXTRACT CA. OF FUNDUS
RETICULOCYTES 131.3 gms.

CHART 3.—Failure of response to human liver extract from a case of carcinoma of the pylorus, and response to liver extract from gastric carcinoma not involving the pylorus.

The slight elevation of reticulocytes which occurred on the fifth day following injection of the liver extract was traced to the accidental inclusion of liver in the diet. (This is an explanatory addendum to Fig. 3.)

EXPERIMENT 4.—*Extract from the liver of a patient with carcinoma of the cecum* (A–38–1165). The patient was a markedly emaciated colored female of 67, who complained of abdominal pain, vomiting, and loss of weight over a period of 3 months. Hematologic examination revealed 1,900,000 red cells per c.mm. The necropsy, which was performed 1 hour after death, revealed an adenocarcinoma of the cecum. The gastric mucosa was slightly atrophic but was otherwise normal.

The patient used for the determination of the antianemic principle in the liver was a white male of 74 with a typical Addisonian pernicious anemia. Hematologic examination revealed 1,500,000 red cells and 6000 white cells per c.mm. The hemoglobin value (Hellige) was 7.2 gm. (49%). The mean corpuscular volume was 127 cu. microns and the mean corpuscular hemoglobin 49 micromicrograms. The average percentage of reticulocytes was 0.8. No free hydrochloric acid was present in the gastric secretion either before or after the administration of histamine. Bone marrow puncture revealed numerous megaloblasts.

The intramuscular injection in a single dose of 16.5 cc. of liver extract (representing 150.2 gm. of whole liver) produced a reticulocyte response which reached a peak of 18.8% on the seventh day following. On the tenth day, when the reticulocyte count was 2.8%, the administration of 30 units of commercial liver extract (Lilly) caused another rise, which reached a peak of 16% on the eighth day following (Chart 4).

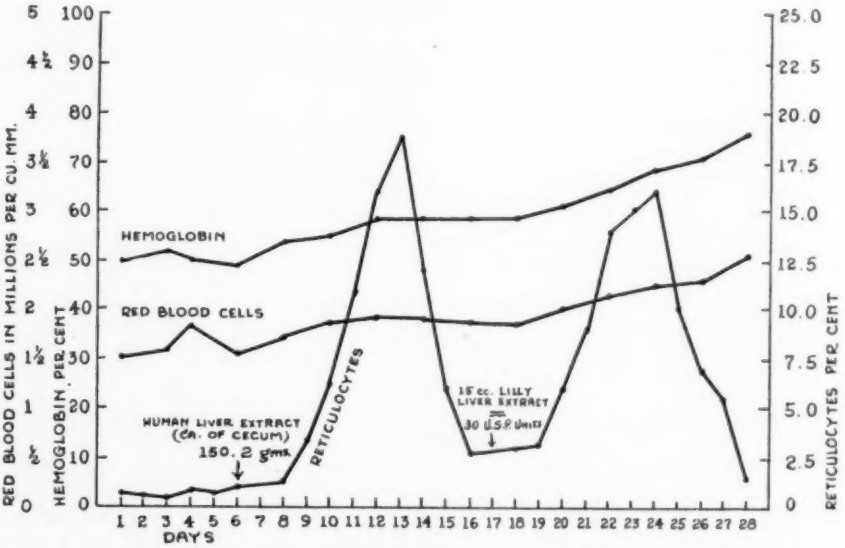
RED BLOOD CELLS IN MILLIONS PER CU. MM.
HEMOGLOBIN PER CENT
RETICULOCYTES PER CENT
HEMOGLOBIN
RED BLOOD CELLS
RETICULOCYTES
HUMAN LIVER EXTRACT (CA. OF CECUM) 150.2 gms.
15 cc. LILLY LIVER EXTRACT = 30 U.S.P. UNITS
DAYS

CHART 4.—The response to human liver extract from a case of carcinoma of the cecum.

Summary. An extract prepared from the liver of a patient whose death was due to scirrhous carcinoma of the pars pylorica failed to produce a reticulocyte response when administered to a patient with typical Addisonian pernicious anemia in relapse. A control extract prepared from the liver of a patient whose death was due to cerebral hemorrhage caused a stimulation of erythropoiesis in the same subject.

An extract prepared from the liver of a patient whose death was due to gastric carcinoma which involved the whole stomach except for a portion of the pars pylorica stimulated erythropoiesis in a patient with a macrocytic hyperchromic anemia.

The administration of the extracts prepared from the livers of the 2 patients with carcinoma of the stomach to another patient with typical Addisonian pernicious anemia in relapse confirmed the observations just described.

The hematopoietic potency was present in an extract prepared from the liver of a markedly emaciated patient whose death was due to carcinoma of the cecum, as demonstrated by its administration to a patient with typical Addisonian pernicious anemia.

The most active antianemic effect of the gastric mucosa, according to experimental observations, is obtained from the mucosa of the pyloric antrum. It seems significant, therefore, that in the cases herewith reported the antianemic principle was demonstrated to be absent in the liver of the patient whose pyloric mucosa was replaced by neoplastic tissue but to be present in the liver of the patient whose entire stomach, except for the pylorus, was involved by carcinoma.

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FOLLICULAR LYMPHOBLASTOMA (GIANT LYMPH FOLLICLE HYPERPLASIA OF LYMPH NODES AND SPLEEN).

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The clinical and pathologic entity variously termed "giant lymph follicle hyperplasia of lymph nodes and spleen," "giant follicular lymphadenopathy" or "follicular lymphoblastoma" was probably first described by Becker[4] in 1901. Descriptions of the condition also were made by Foix and Roemmele[8] in 1912, by Kettle[13] in 1920 and by de Jong[12] in 1921. In this country the disease was not generally recognized by the medical profession until Brill, Baehr

and Rosenthal[5] reported 2 cases in 1925. In this first American report the investigators stated that the hyperplastic process was apparently benign. In 1927 Symmers[16a] reported 3 cases and also stressed the relative benignity of the disease. In the same year, however, Baehr and Rosenthal,[2] in another report, revised their conception as to the benignity of the condition and called it "malignant lymph follicle hyperplasia."

Again, in 1931, Baehr and Rosenthal in collaboration with Klemperer discussed the condition and stated that the disease is a form of lymphosarcoma which deserves to be distinguished from other varieties and proposed the term "follicular lymphoblastoma" to designate the condition. The chief characteristics of this disease were outlined as follows: 1, lymphadenopathy due to hyperplasia of the germinal centers of the lymph follicles; 2, splenomegaly due chiefly to enormous enlargement of Malpighian bodies; 3, absence of abnormal cells in the blood; 4, absence of anemia and cachexia; 5, tendency toward development of serous effusion in pleural and peritoneal cavities; 6, absence of involvement of tonsils and lymphatic apparatus of the gastro-intestinal tract; 7, tendency to lymphatic infiltration in the lacrimal gland, resulting in unilateral exophthalmos, and 8, multicentric origin throughout the body in the lymph follicles, whereas lymphosarcoma arises monocentrically and spreads by lymphatic extension.

In addition to the aforementioned contributions, Ikeda,[10] Terplan,[17] Ross,[15] McNee,[14] Cabot[6] and Ewing and Fein[7] have reported cases. Symmers[16b] recently has reviewed 25 new cases of giant lymph follicle hyperplasia. The termination of the disease in some of these cases was interesting. In one of them, necropsy revealed necrotic folliculitis of the lymph nodes. In 7 cases, polymorphous-cell sarcoma had developed. In 7 others, the condition was associated with Hodgkin's disease and in 4, with lymphatic leukemia.

The present report is based on a review of cases reported in the literature, together with a clinical and pathologic study of 13 cases in which the patients were seen at The Mayo Clinic. Of the latter, 7 of the patients have died. In 3 cases, necropsy was performed; in 8, the lymph nodes, and in 2, both lymph nodes and spleen, were available for histologic examination. Only 1 illustrative case will be reported, since the most important data from all of them have been arranged in Table 1.

Illustrative Case.—A white farmer, aged 42, registered at the clinic on May 9, 1935. He complained of shortness of breath and weakness of 8 months' duration. On further questioning it was learned that he had suffered from dysentery for years following his service in the United States Army. In 1923, he had noticed nodules as large as peanuts in his groin. In 1927, a mass about the size of a hen's egg had appeared in the right axilla and another developed in the left side of the neck; it was about as large as a walnut. All these signs gradually had disappeared until January, 1932, when the patient consulted his local physician because of generalized

TABLE 1.—CLINICAL DATA OF 13 PATIENTS WHO HAD FOLLICULAR LYMPHOBLASTOMA.

Case.	Age at onset and sex.*	Chief symptoms, signs and progress of disease.	Histologic diagnosis.	Reaction to radiotherapy.	Result.	Life duration, yrs.†
1	31M	Ing. lymphadenopathy . 1923 Ax. and cerv. lymphadenopathy . . . . 1927 Splenomegaly . . . 1932 Hepatomegaly, loss of appetite, 1 yr. . . 1934 Root pains 1935	Infl. lymph node (elsewhere) 1932 Infl. lymph nodes (elsewhere) . 1935 F.L. of lymph nodes . . . 1935 Ly.sa. of lymph nodes . . . 1936	Excellent	Gen. involvement. G.I. hemorrhage Death 1937; Ly.sa.	14
2	60M	Asymptomatic except for discomfort of ing. hernia	F.L. (necropsy). Lymph nodes and spleen, G.I. tract also involved	None given	Died 18 days after hernioplasty, of pul. embolism	?
3	44F	Progressive weakness . 1935 Pain in L. U. quadrant, 15 lbs. wt. loss, dyspnea, palpitation, gen. lymphadenopathy, splenomegaly, hepatomegaly, anemia, bilat. hydrothorax 1936	F.L. cerv. lymph nodes . . . 1936 Necropsy . . 1937	Leukopenia developed	Gen. involvement. Death 1937	1¾
4	49M	Wt. loss and weakness . 1917 Cerv. lymphadenopathy, anemia, splenomegaly 1918	F.L. (cerv. lymph node) . . . 1918 Also necropsy . 1922	None given	Gen. involvement. Chylothorax. Death 1922	5
5	42M	Weakness . . . . 1930 Splenomegaly, ing. lymphadenopathy . 1931 Tonsillitis . . . . 1933 Pains, back and legs . 1934 Gen. lymphadenopathy, exophthalmos . . . 1937 Nausea, vom., back pain 1938	F.L. of spleen . 1931 Tonsils . . . 1933 Lymph nodes . 1936 Ly.sa. . . . 1937	Excellent	Gen. involvement. G.I. hemorrhage. Death 1938	7
6	56F	Abdominal mass . . 1931 (retroperitoneal nodes) Nausea, vom., diarrhea . 1936	F.L. mesenteric lymph node . 1931	Excellent	Gen. involvement Anemia. Death 1938	7
7	48M	Bilat. cerv. nodes . . 1929 A dominal distention . 1931 Dull pain, numbness . 1931 Numbness, tingling of feet . . . . . 1931 Weakness, wt. loss and upper abd. pain . . 1931	F.L. cerv. lymph node . . . 1932	No improvement	Death September 1932	3¼
8	36M	Weakness, epigastric distress . . . . . 1932 Fever . . . . . 1933 Lymphadenopathy, splenomegaly, hepatomegaly, anemia . . 1933 Tonsillitis 1933	F.L. of spleen and lymph nodes and tonsils . . 1933	Excellent	Gen. involvement	7
9	47F	Cerv. and ax. lymphadenopathy . . . . 1935 Gen. lymphadenopathy 1936	F.L. cerv. lymph node . . . 1936	Excellent	Asymptomatic 1939. Few small post. cerv. nodes on left side	4

* Mean age at onset was 47.7 years.

† Mean duration of life after onset for 6 patients who died of the disease was 6.3 years.

F.L. = Follicular lymphoblastoma. Ly.sa. = Lymphosarcoma.

TABLE 1.—CLINICAL DATA OF 13 PATIENTS WHO HAD FOLLICULAR LYMPHOBLASTOMA. (*Continued.*)

Case.	Age at onset and sex.*	Chief symptoms, signs and progress of disease.	Histologic diagnosis.	Reaction to radiotherapy.	Result.	Life duration, yrs.†
10	60M	Cerv. lymphadenopathy 1936	F.L. of submax. lymph node .	None given	Asymptomatic(?)	3
11	49M	Cerv. lymphadenopathy 1930 "Occ. bilious attacks" Epigastric mass . . . 1931 Pleural effusion . . . 1931	F.L. cerv. lymph node . . . 1931	Excellent	Asymptomatic 1939	8+
12	42F	Cerv. lymphadenopathy 1932	F.L. cerv. lymph node . . . 1932	Excellent	Heavy feeling in lower abd., otherwise asymptomatic 1939	7
13	54M	Gen. lymphadenopathy Aug. 1939	F.L. cerv. lymph node . . . 1939	Excellent	To return for checkup	?

* Mean age at onset was 47.7 years.
† Mean duration of life after onset for 6 patients who died of the disease was 6.3 years.
F.L. = Folicular lymphoblastoma. Ly.sa. = Lymphosarcoma.

lymphadenopathy. The physician's report stated that the nodes were freely movable, were not tender or confluent, and were not attached to the skin or underlying tissue. The spleen was enlarged and was palpable 3 to 4 fingerbreadths below the costal margin. Results of hematologic examination were negative. A node was removed by the local physician and was reported by a pathologist to be inflammatory. Shortly before the patient came to the clinic another node had been removed elsewhere and histologic examination disclosed chronic lymphadenitis.

On physical examination the patient was found to be pale with hemorrhagic spots over the chest. The cervical, submental, epitrochlear and inguinal lymph nodes were enlarged. The spleen was enlarged and extended 2 inches below the level of the umbilicus. The liver also was moderately enlarged.

A lymph node, removed from the left supraclavicular region on June 4, 1935, showed a striking increase in the number and size of the follicles, with corresponding compression of the interfollicular tissue (Fig. 1, *a* and *b*). The cells of the follicles contained large pale-staining nuclei and few mitotic figures (Fig. 1, *c*). There were zones containing smaller lymphocytes about the follicles. There was slight proliferation of capillaries in the interfollicular zone. The capsule was not invaded. Because of the long history of this patient and the physical observations and since the histologic picture was that of giant lymph follicle hyperplasia, a diagnosis of follicular lymphoblastoma was made.

Roentgen therapy was administered for the lymphadenopathy and splenomegaly and the patient was dismissed on June 14, 1935. He improved and was well for several months, but returned at numerous times the following year because of pain in various situations. Roentgen therapy gave him much relief.

On Sept. 25, 1936, a lymph node removed from the left epitrochlear region showed hardly any traces of the architecture characteristic of giant lymph follicle hyperplasia. Most of the follicles had fused with one another

and had resulted in complete destruction of the architecture (Fig. 1, *d*). There was invasion of the capsule and surrounding tissue.

The patient's last admission to the clinic was on Dec. 22, 1937, when he was suffering from gastro-intestinal hemorrhage. Transfusions of blood were necessary. A letter from his local physician stated that the patient died on Dec. 27, 1937, the cause of death apparently being massive gastro-intestinal hemorrhage. Necropsy was not performed.

COMMENT. This case illustrates the relatively benign course that the disease in question may take. Lymphadenopathy had extended over a period of 14 years and was marked by remissions and exacerbations. Similar cases have been noted by other workers and originally led Baehr, Brill and Rosenthal to believe that the condition was benign, although they later changed their opinion. The present case also emphasizes the difficulties that may confront the pathologist in making a diagnosis. The histologic appearance of tissue first removed elsewhere, and also the tissue later removed at biopsy at the clinic, was that of giant lymph follicle hyperplasia. A somewhat similar appearance is often seen, however, as a reaction of lymph nodes to toxic or inflammatory conditions and it can be understood how easy it would be to err in the histologic diagnosis if the histologist were unfamiliar with the disease.

Clinical Features. Fifty-nine cases were collected from the literature and analyzed together with the 13 cases referred to herein, making a total of 72 cases. The mean age of all these patients was 39.3 years. The oldest patient was 77, the youngest 2 years. Only 9 patients, however, were less than 30 years of age. There were 47 males and 25 females.

The disease under consideration generally begins insidiously. Often, the first symptom is enlargement of local lymph nodes unaccompanied by any feeling of ill-health on the part of the patient. This has been emphasized by many investigators. The disease produced no symptoms for 1 of our patients (Case 2) and was unsuspected until it was disclosed at necropsy (Table 1). Absence of anemia or cachexia may mislead the physician into suspecting an inflammatory or toxic agent as the cause of the lymphadenopathy. An interesting observation in our present series was the fact that 4 patients complained of weakness as one of the symptoms first noticed. This weakness was accompanied by loss of weight in only 1 instance.

Of all cases reported, including the present series, the regional lymph nodes were first enlarged in 33, whereas in 32 cases there was more or less generalized involvement of lymph nodes at the onset of the disease.

The nodes vary in diameter from 1 to 5 cm. or more. In the early stages of the condition, at least, they are discrete, movable and painless. Later they are very closely packed and appear to be confluent. As shown by our Case 1 and other cases reported by

Symmers, the nodes may diminish spontaneously in size or disappear for a time.

The cervical nodes are generally the first to be involved, although the disease may appear earlier in the axillary or inguinal group of nodes and in one of our cases the mesenteric nodes were apparently the first to be affected. An interesting observation in the present series in this connection is the frequency with which the patients complained of gastro-intestinal symptoms. Seven patients had such complaints as a sensation of fullness, belching, gas, loss of appetite, constipation and diarrhea. These symptoms, in 3 patients, were probably related to the presence of an enlarged spleen. The possibility that these symptoms were due, in some cases, to involvement of the mesenteric and retroperitoneal lymph nodes with subsequent disturbances in lymphatic absorption and drainage also must be considered. These nodes were found to be involved in the patients who had these symptoms.

Splenic enlargement also is a frequent occurrence. It was present in 44 cases out of the 72 cases (including our 13 cases) reported in the literature (61.1%). In some cases reported in the literature it was the first symptom and was unaccompanied by appreciable lymphadenopathy. Of the cases in which patients came to necropsy, the spleen was enlarged in all. Hepatic enlargement does not occur so frequently as splenic and was described in only 8 cases.

The tendency toward development of serous effusion in pleural and peritoneal cavities has been mentioned as a characteristic feature of this disease. Ascites was present in 5 and hydrothorax in 9 cases reported in the literature. Exophthalmos as a result of infiltration of the lacrimal gland has been described by Baehr[1] as occurring in 4 of the 19 cases which he discussed. It afflicted only 1 patient in our series (Case 5) and has not been described by other workers (Table 1).

Baehr, Rosenthal and Klemperer[3] emphasized the absence of involvement of tonsils and the lymphatic apparatus of the gastro-intestinal tract. Tonsillar enlargement and tonsillectomy are recorded concerning some of the cases in the literature but no descriptions have been provided of the histologic appearances of removed tissue. In our own series there were 2 cases (Cases 5 and 8) in which involvement of the tonsils occurred, and 1 case (Case 2) in which the lymphatic tissue of the gastro-intestinal tract was found to be involved at necropsy (Fig. 2, *a*).

Hematologic Observations. Anemia is not often encountered at the onset of the disease being described. It was mentioned in only 6 cases reported in the literature and found in only 3 of our cases (Cases 3, 4 and 8). It is of the hypochromic variety and is not as a rule severe. The leukocyte count is generally normal but slight leukopenia may be present. Studies of the blood smears revealed no significant abnormalities among our patients. Symmers, how-

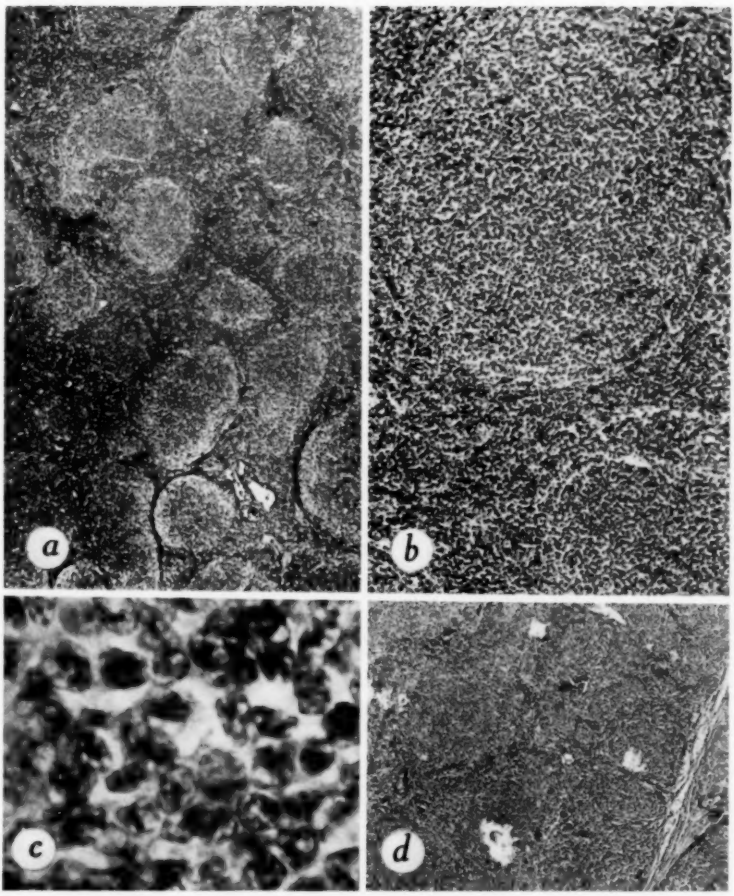

FIG. 1.—Histologic sections of lymph nodes from Case 1; *a*, left supraclavicular node removed June 4, 1935, with large hyperplastic follicles (hematoxylin and eosin ×100); *b*, same section shown in Figure 1*a* (×100); *c*, structure of the nuclei in a follicle (×1000); *d*, left epitrochlear lymph node, removed September 25, 1936; lymphosarcoma (hematoxylin and eosin ×25).

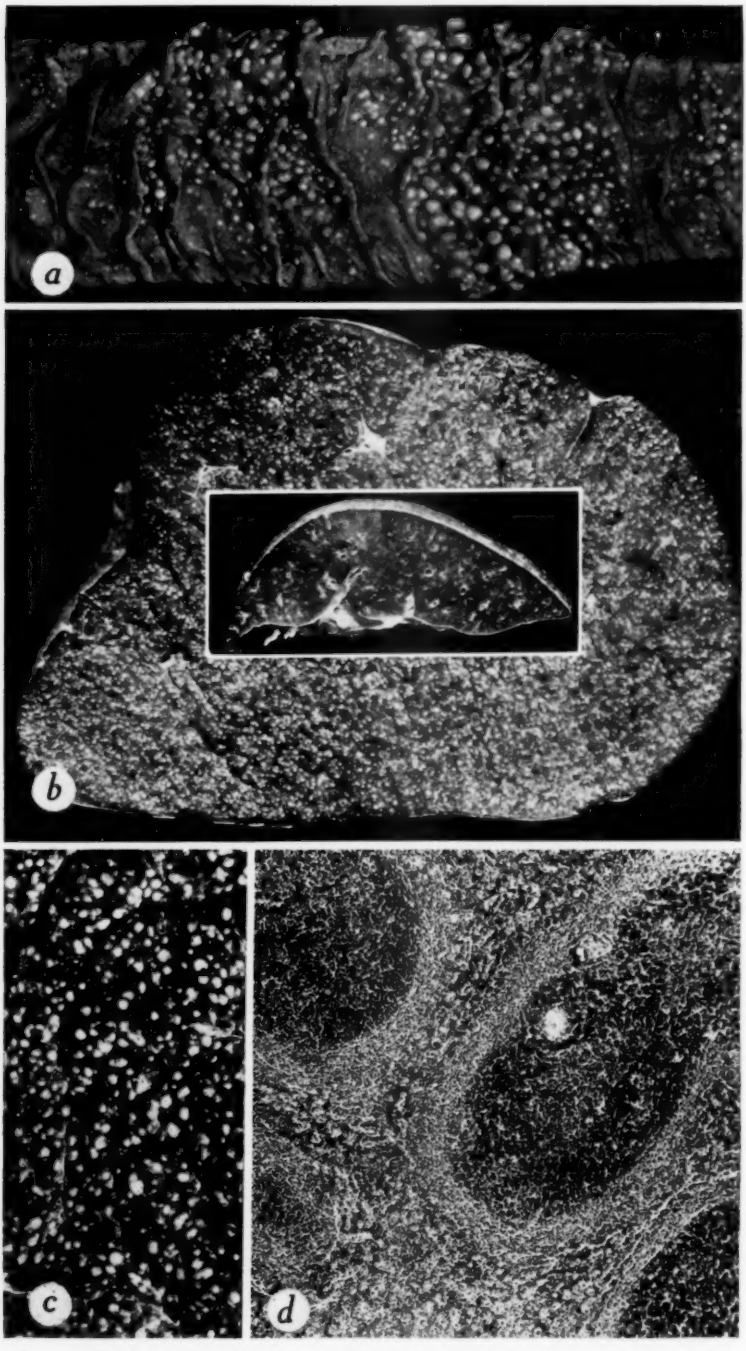

FIG. 2.—Follicular lymphoblastoma; *a*, segment of ileum (Case 2); *b*, cut surface of spleen (Case 3) compared with a normal spleen; *c*, close-up photograph of spleen (Case 3); *d*, photomicrograph of spleen (Case 3) (hematoxylin and eosin ×32).

ever, has reported 3 cases of the disease in which lymphatic leukemia developed and 1 in which the disease apparently was associated with lymphatic leukemia.

Duration. Data concerning the duration of the disease were available in 53 cases, including 11 reported at this time. The average duration of life after appearance of the disease in 24 patients who were living at the time they were reported on was 4.6 years. Two of the patients had been living 17 years. The average duration for 29 of those who had died was 4.8 years. All workers agreed that this disease offers a better prognosis than do other varieties of lymphosarcoma. According to Baehr the average duration for patients who have other types of lymphosarcoma, excluding involvement of the gastro-intestinal tract, was 11 months. According to Jackson,[11] the average duration for a patient who had Hodgkin's disease was 2.5 years, whereas that for one who had giant follicle lymphoma (follicular lymphoblastoma) was 4 years.

Reaction to Radiotherapy.—Workers generally agreed that follicular lymphoblastoma responds more readily to Roentgen therapy than does any other neoplastic disease of the lymph nodes. The enlarged nodes and spleen often have been described as "melting away" after the first treatment. Of 44 patients reported on in the literature, including the present series, 38 responded well to radiotherapy, whereas only 6 responded poorly. Unfortunately, after repeated treatments the disease no longer responds so readily as at first and finally the Roentgen rays fail to affect the progress of the disease at all. No permanent cures have as yet been reported.

Gross Pathologic Anatomy. Although almost any organ may become involved in the pathologic process of the disease in question, the lymph nodes and spleen are generally the first structures to be involved or to reveal the most marked and typical changes. Characteristic lesions have been described less frequently as occurring in the liver and bone marrow.

Usually, the lymph nodes are firm in consistency and in the cut section the enlarged follicles can be seen by the naked eye. The capsule generally is not invaded early in the disease.

The spleen usually is greatly enlarged. The average weight of the spleens in 19 cases reported in the literature, including the present series, was 1665 gm. The largest, that described by de Jong, weighed 6500 gm.; the largest spleen in our series weighed 2300 gm. The spleen is firm and may be covered by a hyaline substance. Adhesions are frequently present. The purplish-red cut surface of the organ is studded with numerous, pale, grayish, somewhat raised portions varying from 1 to 3 mm. in diameter (Fig. 2, *b* and *c*). Many of these raised structures are greatly hypertrophied Malpighian corpuscles (Fig. 2, *d*).

Histopathology. Histologic examination of lymph nodes removed in the early stage of the disease reveals a striking increase in the

size and number of the follicles (Fig. 1, *a*). The follicles vary in size but nearly all are larger than normal. Variation in shape may or may not be marked. They are mostly round but may be ovoid, hook or clover-leaf-shaped. The central portions generally consist of larger cells with large faintly-staining nuclei and numerous mitotic figures. These cells are generally regarded as lymphoblasts but in some instances they appear to arise from reticulum cells. About the periphery of the follicles small deeply-staining lymphocytes are densely packed and may appear to be arranged in circumferential rows. Occasionally, the enlarged follicles consist entirely of small or medium-sized lymphocytes which are closely packed. By the use of silver impregnation methods only relatively few reticulum fibrils can be demonstrated in the follicles.

Because of the tremendous increase in size and number of the follicles, the interfollicular zones are generally narrowed and compressed. The predominating cell in the interfollicular tissue is the lymphocyte, but there often is increased proliferation of capillaries and endothelial cells. The increase in the number of capillaries may be more apparent than real because of the compression of the interfollicular zones by the rapidly growing follicles. The endothelial proliferation, however, is definite. These cells often fill the lumens of the capillaries and in some instances migrate away from the vessel and lose their attachment to it. The lymphatic sinuses are always narrowed and may be obliterated. By silver impregnation methods an apparent increase in the number and size of the reticulum fibers can be demonstrated.

In some cases, the involved lymph nodes maintain the same histologic appearance throughout the disease. In 2 of our cases, later biopsies revealed the histologic picture of lymphosarcoma. Traces of the follicular structure still could be found in these lymph nodes, however.

In sections of the involved spleen there is a striking numerical and dimensional increase in the Malpighian bodies as well as numerous independent nodular proliferations of lymphocytes which may or may not be connected with Malpighian bodies (Fig. 2, *d*). The increase in the size of these structures can be attributed, in some cases, to the proliferation of small, deeply-staining lymphocytes and in other cases to the proliferation of larger cells with large, pale-staining nuclei. Both types of cells are found, however, in all Malpighian bodies and nodules in varying numbers. Mitotic figures are not infrequent. As a result of the increase in size and number of these structures, compression of the interfollicular splenic pulp and sinuses is common. Occasionally, there is an apparent proliferation of capillaries, in both follicles and pulp. The littoral (reticulum) cells lining the sinuses also, occasionally, appear to be increased.

Unfortunately, the histologic appearance of follicular lympho-

blastoma in its early stages is sometimes mistaken for "inflammatory" hyperplasia of the secondary nodules of lymph nodes. The similarity is, however, only a superficial one and a distinction between the two conditions is generally not difficult to make if the histopathologist is familiar with follicular lymphoblastoma and its histologic characteristics.

To establish histologic criteria which would enable the histopathologist to differentiate inflammatory hyperplasia of the secondary centers from follicular lymphoblastoma, a study was made of biopsied specimens of lymph nodes from 50 cases in which a diagnosis of inflammatory lymphadenopathy had been made. In each case the diagnosis had been confirmed by the subsequent clinical course of the patient. In none of these cases was there any difficulty in distinguishing the histologic appearance of the nodes from that of follicular lymphoblastoma. The points which were found to be of value in differentiating the two conditions have been listed in Table 2.

TABLE 2.—HISTOLOGIC DIFFERENCES BETWEEN FOLLICULAR LYMPHOBLASTOMA AND INFLAMMATORY HYPERPLASIA.

	Follicular lymphoblastoma.	Simple hyperplasia of inflammatory or toxic origin.
Follicles	Larger and more numerous	Smaller and less numerous
	Closely packed	Scattered
	Diffuse throughout node	Arranged around cortex in concentric rows
	Frequent in medulla	Few in medulla
	Uniformly large	Vary in size
	Tend to fuse	Are discrete
Interfollicular tissue	Cells densely packed	Cells scattered
	Condensation of reticulum	Loose reticulum
	Sinuses narrowed or blocked	Sinuses open—often dilated
	Slight proliferation of reticular cells	Marked proliferation of reticular cells

The most helpful histologic sign in distinguishing follicular lymphoblastoma from inflammatory hyperplasia was the greater numerical and dimensional increase in the follicles in the presence of the former condition. In addition to this quantitative difference, the tendency of the follicles to fuse with each other and the narrowing and obliteration of the lymphatic sinuses were found to be typical of follicular lymphoblastoma and were very helpful as diagnostic signs. The presence of mitotic figures was of little help. Such figures are as frequently present in one condition as in the other. In occasional cases, in which a conclusion could not be reached, even after careful study, it was found convenient to reserve the diagnosis and to use a non-committal term such as "follicular hypertrophy" to describe the histologic appearance. Further observation and subsequent biopsy generally substantiated the suspicion that we were concerned with an early instance of follicular lymphoblastoma.

Classification of Follicular Lymphoblastoma. Baehr, Klemperer and Rosenthal stated in 1931 that follicular lymphoblastoma is a form of lymphosarcoma which deserves to be distinguished as a pathologic entity and that it may form a connecting link between systemic hyperplasia of the lymphatic tissue (aleukemic lymphadenosis) and lymphosarcomatosis. Symmers in 1938 reported 3 cases of giant follicular lymphadenopathy in which the condition terminated as lymphatic leukemia, and this would seem to support the conception of Baehr, Klemperer and Rosenthal. Ghon and Roman[9] in 1916 described the tendency toward formation of new follicles in 10 cases of lymphosarcoma but the condition in these cases did not manifest itself as does follicular lymphoblastoma, either clinically or anatomically. As has been pointed out by Baehr and associates, follicular lymphoblastoma has a multicentric origin in the lymph follicles, throughout the body, whereas lymphosarcoma arises monocentrically and spreads by lymphatic or hematogenous extension. Ross thought the condition to be hyperplasia affecting undifferentiated cells with unrestricted potency for differentiation, and has classified it as "lymphoid reticulosis." This point of view assumes that the reticular cells are chiefly involved in the proliferative process, whereas most workers believe that homoplastic proliferation of lymphocytes is the more important process. Symmers stated that giant follicular lymphadenopathy is probably of inflammatory or toxic origin. This conception receives some support from the relatively benign early course of the disease, but it does not explain the fatal termination of the condition among patients who have been followed over a long period of time.

The conception of Baehr and associates of the position of follicular lymphoblastoma as a connecting link between systemic hyperplasia of the lymphatic system and lymphosarcomatosis has much to recommend it. It must be pointed out, however, that follicular lymphoblastoma is more amenable to Roentgen therapy and generally runs a much longer course than either aleukemic lymphadenosis or lymphosarcomatosis.

Summary and Conclusions. A clinical and pathologic entity variously called "giant follicle hyperplasia of lymph nodes and spleen," "giant follicular lymphadenopathy" and "follicular lymphoblastoma" has been described in the literature in recent years with increasing frequency. The condition is characterized by an insidious onset with regional or general lymphadenopathy, splenomegaly, the absence of anemia or abnormal cells in the blood and by the great radiosensitivity of the lesions. The average duration of life after the appearance of the disease is 4.5 years, but 2 patients have lived as long as 17 years with this disease.

The characteristic histologic changes occurring early in the disease consist of an increase in the number and size of the follicles of the lymph nodes and of the Malpighian corpuscles of the spleen.

There is a tendency toward fusion of the follicles and the lymphatic sinuses are generally narrowed or obliterated.

There is a superficial resemblance between the histologic appearance of follicular lymphoblastoma and the histologic appearance of hypertrophy of the secondary centers of lymph nodes resulting from toxic or inflammatory conditions. The histologic criteria which enable the histopathologist to distinguish the two conditions have been outlined.

In certain rare instances in which the histologic appearance is not typical of either follicular lymphoblastoma or inflammation, it may be wise to reserve diagnosis and merely to use a descriptive, noncommittal term, such as "follicular hypertrophy," to denote the condition. Subsequent observation and biopsy frequently will bear out the suspicion that the condition in question is an early instance of follicular lymphoblastoma.

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THROMBOSIS OF THE AXILLARY AND SUBCLAVIAN VEINS.

WITH A NOTE ON THE POST-THROMBOTIC SYNDROME.

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THROMBOSIS of the axillary and subclavian veins is an uncommon condition. From a review of the literature of the last 50 years, we were able to collect less than 150 cases. However, the number of reports have been steadily increasing, and undoubtedly it is more frequent than a study of the records leads one to believe. The fact that only 23 articles have dealt with more than one case shows that the experience of a single author has been limited. The bases for this report are the observations on 17 cases of thrombosis of the axillary and subclavian veins. In addition to the usual clinical data, the

venous pressures of the normal and affected extremity have been recorded, and venographs demonstrating the point of obstruction and outlining the collateral circulation have been made in most of the cases. From these studies certain facts have been learned concerning the basic pathology, the altered physiology during the early and late stages, the development of collateral venous circulation, and finally the end results of this condition.

Acute thrombosis of the axillary and subclavian veins produces a typical symptom complex, regardless of the etiology of the thrombosis. The cardinal symptoms are pain in the arm and shoulder; massive pitting edema of the entire extremity; weakness and partial loss of function of the arm; preservation of the radial pulse; elevation of systolic pressure on the affected side; palpable, tender, cordlike swelling along the course of the brachial, basilic and axillary veins; marked elevation of the local venous pressure; and a decrease in the oxygen content of venous blood of the affected arm.

The essential pathology of thrombosis of the axillary and subclavian veins is that of obstruction of the return blood flow from the hand and arm, vasospasm, an increase in local venous pressure, and an escape of fluid into the tissue. Many writers have used the term "primary thrombosis of the axillary vein," but, as a matter of fact, the thrombosis is seldom confined to the axillary vein alone. In almost all instances it involves the entire axillary, portions of the subclavian, the basilic and brachial veins, occasionally the external jugular, and rarely the internal jugular vein. The entire thrombus may be absorbed, or it may become organized and permanently obstruct the vessels. There may be a recanalization of the lumen, but this is usually incomplete, and the return circulation must be carried on by the newly developed collaterals.

There are several forms of thrombosis of the axillary and subclavian veins. Although some of the etiologic factors have not been definitely established in these several forms, the following classifications seem complete enough for practical purposes. 1. PRIMARY THROMBOSIS: (*a*) Thrombophlebitis (Bacterial); (*b*) Phlebothrombosis (Non-bacterial, traumatic or effort thrombosis). 2. SECONDARY THROMBOSIS: (*a*) Thrombophlebitis from regional infection; (*b*) Thrombosis from malignancies of the axilla and chest. 3. POST-THROMBOTIC SYNDROME.

The 17 cases which we have had the opportunity to study at the Charity Hospital, New Orleans, and at Gallinger Municipal Hospital, Washington, D. C., provide examples for each of the types in the above classification. Four were classified as primary and one as secondary thrombophlebitis. Four were classified as primary phlebothrombosis. Eight of the cases fell in the group of secondary thrombosis from malignancies of the chest and axilla.

Thrombophlebitis. True thrombophlebitis of the axillary and subclavian veins is indeed a rare condition when compared with the

frequency of this disease in the vessels of the lower extremities. Thrombophlebitis presents definite constitutional and local signs of inflammation. The body temperature is elevated, the pulse is accelerated, and there is a leukocytosis. The skin over the involved veins is warm, reddened, tender to touch, and painful on manipulation. Pitting edema of the hand and entire arm develops rapidly. It occurs most often in cardiac patients in whom there is a slowing of the venous blood flow (Fig. 1). The phlebitis may be secondary to an infection in the region of these veins or their tributaries. Blumer[3] reported a case secondary to pulmonary tuberculosis. Jakobson[8] reported a case following influenza. McGoogan and Simmons[11] described a case of thrombophlebitis beginning in the left side of the neck and extending into the subclavian and axillary veins in a patient during the puerperium.

Case Reports. Case 1.—In one of our own cases the thrombophlebitis was secondary to a skin infection of the neck. A small furuncle developed over the external jugular vein, and the infection extended to the vein wall and produced a thrombosis. The thrombus then spread from the external jugular to the subclavian, axillary, basilic and brachial veins. This patient was a cardiac in a state of congestive failure. She presented the typical findings of acute thrombophlebitis of the veins of the upper arm, axilla and neck, with massive edema of the arm. There was a mild constitutional reaction; temperature, 101° F., and a leukocytosis of 14,000.

Case 2.—Our second patient had had hypertension for many years. Shortly before onset of the axillary and subclavian vein thrombosis she had "chills and fever." The following day she awoke with acute swelling of the left arm. There was increased heat, redness and tenderness along the veins of the upper arm, axilla and neck. She had a febrile temperature and leukocytosis.

Case 3.—The third case was also a hypertensive patient, and in addition was in a state of congestive failure. After being confined to bed for several days, she developed thrombophlebitis of the veins of the left side of the neck which gradually extended to the subclavian and axillary veins. She exhibited the cardinal symptoms of acute thrombophlebitis, including fever and leukocytosis.

Cases 4 and 5.—The fourth and fifth cases were quite similar in character, occurring in elderly white females several weeks after the onset of acute congestive cardiac failure.

Four of these recovered from the acute stage of the thrombophlebitis, but later showed some residual signs and symptoms. One died of congestive failure.

In thrombophlebitis of the axillary and subclavian veins, the signs of the acute infection usually subside within a few days. The edema gradually disappears as the collateral circulation develops (Fig. 2). While a few of the reported cases have died, the cause of death has been the associated disease and not the thrombosis. Embolism rarely follows.

There are probably two reasons why thrombophlebitis is so infrequent in the upper extremity. The most important is the rapid emptying of the venous system of the arm by almost continuous

use of the limb. The second factor, which to me seems important, is the length of the course through which the blood must flow. The distance of the circuit in the upper extremities is so short that stasis is unusual. For whatever reasons, it is an established fact that true thrombophlebitis of the axillary and subclavian veins is indeed a rare disease.

FIG. 1.—Edema of arm from acute thrombosis of axillary and subclavian veins in a cardiac patient.

Primary Phlebothrombosis (Traumatic or Effort Thrombosis). By phlebothrombosis is meant a sterile or non-bacterial form of thrombosis. This is by far the most common form of thrombosis of the axillary and subclavian veins. In this group we have included the so-called "effort type," as well as all cases resulting from direct and indirect trauma to the vein wall, the intima, the valves or adjacent tributaries. The symptoms of phlebothrombosis are identical with those of true thrombophlebitis, except that the local and constitutional signs of inflammation are absent. The onset is usually quite acute, but may be gradual. Pain is the first symptom. It begins as a "sticking" or "stinging" type, involving the entire arm and shoulder girdle. Swelling of the arm and hand develops rapidly, so that in the course of a few hours the entire extremity is enormously enlarged. There is an associated arterial spasm which may cause the

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LEGENDS FOR FIGS. 2 AND 3.

FIG. 2.—Venograph showing the developing venous collaterals in a case of thrombophlebitis of the axillary and subclavian veins; 10 days after onset.

FIG. 3.—Collateral venous circulation following permanent occlusion of the axillary and subclavian veins, from primary phlebothrombosis.

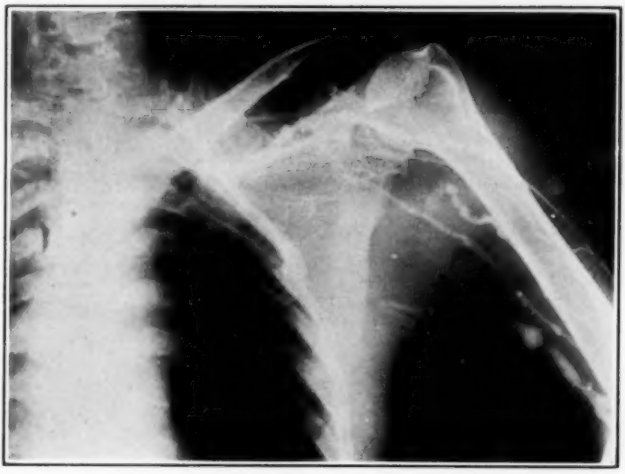

FIG. 2.

FIG. 3.

FIG. 4.—Massive edema of arm and hand from thrombosis of the axillary and subclavian veins in a case of recurrent carcinoma of the breast. The thrombosis followed invasion of the axillary by the tumor cells.

FIG. 5.—Venous collateral circulation over the arm and shoulder after occlusion of the subclavian vein by thrombosis secondary to metastatic carcinoma from lung.

hands to feel cold and numb and produce a slight cyanosis of the finger tips. The extremity is perfectly useless, and the patient supports it with his normal limb. The arterial pulse can be easily palpated. Along the inner surface of the upper arm a firm, tender, cordlike mass can be felt extending up through the axilla and to the chest wall. Usually this cord involves the basilic, the brachials, the axillary, and often the external jugular veins. The course of events is quite typical. The maximum swelling is usually reached within 24 hours after onset and persists from a few days to several weeks. As the edema subsides, there is evidence of superficial venous collaterals developing over the upper arm, shoulder and anterior part of the chest wall (Fig. 3). From this stage on the cases vary considerably and will be discussed later.

The explanation of the development of thrombosis following a direct crushing or contusing injury to the axillary vein is obvious. However, only a very few cases have resulted from such an accident. In reviewing the reported cases one is immediately struck with the great variety of circumstances under which the condition develops. It occurs usually in healthy individuals. The right arm is most frequently involved. There has been no uniformity as to the type of trauma, the mode of exercise or position of the arm at the time of injury. It has followed indirect trauma, such as a fall on the shoulder; and direct trauma, such as a contusion over the axillary region. It has followed the simple task of stirring pudding. It has resulted from such violent exercise as rowing a boat. In many, the thrombosis occurred during the patient's sleep and in whom there was no preceding history of trauma or any unusual strain.

Cases 6 to 9.—Four of our cases have been classified as phlebothrombosis. In one, the thrombosis occurred after sleeping with the arm extended upward under the head. In another, it followed a hard day's work at washing clothes. In the third case, there was no history as to preceding effort or strain, but there was no constitutional reaction, and the course was typical of phlebothrombosis. The fourth resulted from a severe contusing injury to the upper left arm and shoulder.

Several attempts have been made to explain the mechanism of the injury to the axillary or subclavian veins in the so-called "effort or primary thrombosis," which we prefer to call phlebothrombosis. Von Schrotter, 1884,[13] is credited with first describing this traumatic type of axillary vein thrombosis. He thought that an unusual muscle strain stretched the axillary vein and caused damage to its wall, and thrombosis resulted. He did not consider any peculiar anatomic features that might be at play. Cadenat[4] introduced another factor, that of distention of the vein by respiratory effort; and he thought that this produced an injury to the venous lining. Willan[16] believed that the axillary vein was stretched between the clavicle and the first rib, producing sufficient injury to cause a thrombosis. Lowenstein[10] concluded from his studies on cadavers that there was a two-

fold basis for the development of thrombosis. First, there was a venous stasis or circulation slowing produced by forced expiration that characterized effort. Second, marked abduction or extension of the arm, probably with lateral rotation, produced a pronounced pressure by the costocoracoid ligament on the axillary vein, with resulting changes in the vascular endothelium sufficient to produce thrombosis. Gould and Patey[7] expressed the opinion that the pressure of the subclavius muscle on the axillary vein caused a distention of the vein and then a rupture of the delicate subclavio-axillary valves.

In a previous communication[15] we reported the results of a series of anatomic studies on fresh cadavers which were made with the object of determining the influence of the position of the arm upon the axillary vein. We showed that when the arm was in the abducted position, the point of compression of the axillary vein was over the subscapularis muscle beneath the head of the humerus. By means of venographs we were able to confirm this on the living subject. We also found that there was an actual stretching of the axillary vein proximal to the point of compression. We were unable to produce constriction of the axillary vein at any other point. These findings seem important because they were demonstrated on cadavers before there were any postmortem contractions of the muscles or fixation of the tissues. Furthermore, they were actually observed in the living subject. We were able to confirm Cadenat's suggestion that respiratory effort might cause considerable distention of the axillary vein under certain circumstances. The arm was abducted in order to constrict and fix the axillary vein over the subscapularis muscle. Then axillary venous pressure determinations under forced respiration were recorded. There were wide fluctuations in the pressure, denoting alternate collapse and great distention of the axillary vein. It is conceivable that such sudden stretching of the vein might cause some injury which would lead to thrombosis. In many of the reports it has been shown that thrombosis followed severe exercise in which the respiratory efforts were strained.

A considerable number of cases have resulted from sleeping either with the arm elevated over the head or folded under the body. In these positions the axillary vein may be completely compressed and fixed. Then, due to periodic increase in expiratory effort, the vein may become distended. If it so happens that the blood flow has been retarded by the compression or constriction, damage may result from the overdistention. Another factor probably enters into these cases. When the venous blood flow is obstructed, there is a lowering of its oxygen content. This is a progressive condition: the more complete and the more lasting the obstruction, the greater the fall in the oxygen of the venous blood. This may reach a stage in which the lining cells of the involved vessels are so damaged that physical changes occur from anoxemia and provide a nidus for the

formation of a clot. Furthermore, it is possible that the intimal cells at the constricted area may be injured by the force of the compression.

Some writers have mentioned venospasm as a possible cause of thrombosis. Injury to a vessel, whether it is traumatic, inflammatory or thermal, may cause a spasm or contraction of that vessel. Vasospasm may result from sympathetic irritation. During the period of spasm the lumen of the vessel may be almost occluded and cause a marked retardation of blood flow. If the exciting cause of the venospasm has also damaged the vein wall or its intima, thrombosis might result. It seems that venospasm must be a secondary and not the primary factor in the production of axillary and subclavian vein thrombosis.

From a careful study of the literature and a consideration of our anatomic and clinical studies, it seems reasonable to state that there are no known anatomic peculiarities or blood diseases that predispose to thrombosis of the axillary and subclavian veins. It seems clear that two factors must always be at play in order for an intravascular thrombus to develop. There must be some damage to the vessel, then a slowing down of the blood flow. The injury may be to the valves, the intima, or the entire vein wall may be damaged. It may result from a direct crushing or contusing blow over the veins. It may result from overdistention of the axillary vein from violent respiratory effort, provided the vein is sufficiently compressed at one point so that the blood cannot empty into its tributaries. If the outlet to the tributaries is not obstructed, the results of forced respiratory efforts are expended by allowing a back flow of the venous blood into these vessels, and overdistention is prevented.

Secondary Thrombosis from Malignancies of Chest and Axilla. Secondary thrombosis of the axillary and subclavian veins from malignancies of the axilla and chest has not received sufficient emphasis.[14a] From a study of approximately 60 cases of postoperative edema of the arm (following radical mastectomy for carcinoma of the breast), we found that the cause of the edema was an obstruction of the venous return from the arm in about 90% of the cases. The obstruction in some was the result of scar formation; in others, direct involvement of the axillary or subclavian vein by the carcinoma.

CASES 10 to 14.—In 5 of our cases the cause of the venous obstruction was proved at autopsy to be due to thrombosis of the axillary and subclavian veins (Fig. 4). In some, the carcinoma cells were found to have penetrated the vein wall and invaded the lumen. Around these cells a clot had formed which completely occluded the vessel. In others, the new growth had involved only the wall, and yet the vessel was completely filled with a thrombus, which was firmly attached to the intima. In one, the thrombosis apparently resulted from compression of the veins by enlarged metastatic glands.

CASES 15 to 17.—In 3 other cases in this present series the axillary and subclavian thrombosis was secondary to primary lung carcinoma. The veins were involved in a similar manner to those following carcinoma of the breast (Fig. 5).

We have been particularly concerned in our studies with the development of the collateral venous circulation. By means of venographs we have actually visualized the venous circulation of the involved region in most of the cases. Venographic studies have been made as early as 48 hours after onset, and as late as 22 years following the development of the thrombosis. Therefore, all stages of the process of the formation of collateral circulation have been visualized. From these observations it has been possible to demonstrate the common routes through which the collaterals develop, the approximate rate, and the extent of the collateral formation.

Regardless of the type of thrombosis, the development of collateral circulation follows a more or less definite course, depending primarily upon the extent of the thrombosis (Fig. 6). When it does not extend beyond the axillary vein, the development of the collaterals is rapid. But when the thrombosis is more widespread, the collaterals develop more slowly. The important tributaries taking part in the development of the collaterals are the superficial veins over the anterior shoulder and chest, the veins following the acromiothoracic artery, the long thoracic, and the cephalic vein. Through this last-named vein the collaterals connect with the superficial and deep veins in the neck. The collaterals may cross the midline of the neck and communicate with the veins on the opposite side. The flow may be retrograde, flowing upward through the external jugular to enter the cerebral vessels. The superficial collaterals over the upper arm and anterior chest usually drain into the mammary, acromiothoracic, long thoracic, intercostals, or internal mammary. There are many small collaterals formed directly through the axilla which connect with the subclavian proximal to the occlusion.

In the cases of secondary thrombosis following radical amputation of the breast, there is less chance for the development of adequate collaterals. Due to the nature of the operation, the acromiothoracic, often the long thoracic, and sometimes the cephalic, has been sacrificed. Furthermore, attempts at collateral formation are frustrated because of the formation of scar tissue through which the new veins must grow.

Post-thrombotic Syndrome. Although the acute stages of phlebothrombosis and thrombophlebitis rapidly abate, the altered physiology of the circulation may not be corrected. There may remain sufficient obstruction to the venous return to produce more or less permanent symptoms. To this symptom complex we have applied the term "post-thrombotic syndrome." It results from permanent occlusion of the axillary and subclavian veins by the organization of the thrombus. The severity of the residual symptoms depends

upon the degree of the formation of collateral circulation. As the acute process subsides, there appear newly-developed collaterals over the shoulder and upper arm, and the edema disappears (Figs. 2, 3). There are no further symptoms while the arm is at rest. Following exercise or prolonged use of the involved limb, the patient feels a sense of fullness, weakness, fatigue and actual pain in the arm and shoulder. In some cases there may be a recurrence of the edema following prolonged exercise.

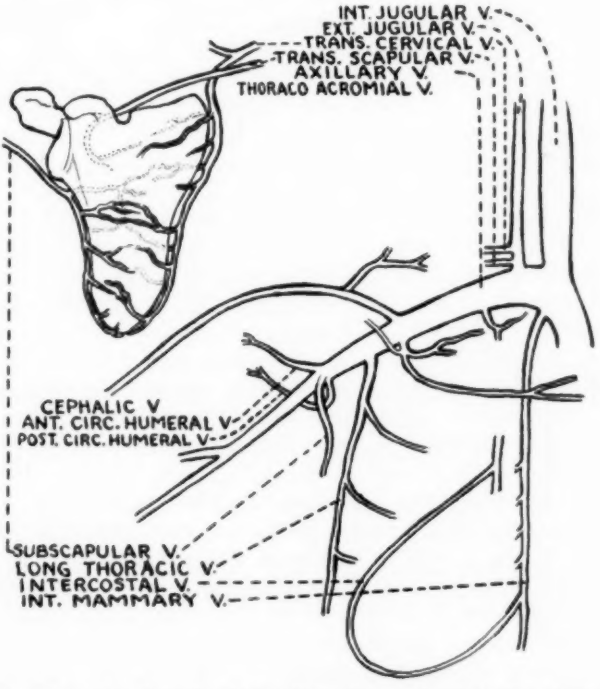

FIG. 6.—Possible routes through which collaterals may develop after obstruction of the axillary and subclavian veins.

There have been only scant reports of follow-up studies after the immediate convalescent or acute stage. However, in those reporting check-up examinations several months to several years after the onset, many have noted this post-thrombotic syndrome. Jeanneney and Mathey-Cornat[9] found pain and swelling in the arm of a patient 6 years after onset of the thrombosis. Firth and Mackay[6] reported a case in which the right arm was involved and in which there was persistent pain after a hard day's work 2 years later. Two years after the onset of the edema in the right arm, the left arm became involved. Ballon[1] reported a case that had discomfort following exercise 20 months after the initial onset. In one of

Clute's[5] cases pain and swelling followed hard labor one year after onset. Baum[2] cited a case with persistent and recurrent edema one year and a half after onset.

In our series of 9 cases of phlebothrombosis and thrombophlebitis, 7 showed residual symptoms after recovery from the acute stage. Three were followed for only 2 months after the occurrence of the thrombosis. One was examined monthly for 6 months. The other 3 were observed at 22, 10 and 6 years, respectively. All 7 presented weakness, early fatigue and pain in the arm after prolonged work or exercise of the involved extremity.

Matas,[12] in an excellent communication on this subject, emphasized the importance of the residual symptoms and discussed the possible medico-legal aspects that may confront one in the management of such cases.

From the venographic demonstrations of the collateral circulation and the venous pressure changes noted in these cases, it seemed clear that the residual symptoms were due to the retardation of the return venous blood flow. Venous pressure studies in a large series of patients with axillary and subclavian vein obstruction following radical removal of the breast had shown that in those with persistent edema of the arm there was marked elevation of the local venous pressure. In this group the average antecubital vein pressure was 530 mm. saline. In one, the pressure reached the amazing level of 1400 mm. saline. In another group of these postoperative cases the patients exhibited edema of the arm only after prolonged exercise of the involved extremity. The edema would subside within 24 hours with complete rest and elevation of the arm. In these the local venous pressure during rest was uniformly lower than in the first group, and in some was within the normal range. It seemed that the collaterals were adequate during rest, but incapable of coping with the great increase in blood flow during exercise.

We then made a series of venous pressure determination on a selected group during active exercise. The antecubital vein was punctured and the pressure recorded at complete rest with the patient in the supine position. Then the patient was instructed to close the hand tightly and immediately release it while the venous pressure apparatus was still in place. This alternate closing and opening of the hand was carried on at a rate of about 30 per minute for a period of 1 to 3 minutes. It was found that during the exercise there was a steady rise in the venous pressure. On stopping the exercise there was a gradual return to pre-exercise level. The same experiments were then conducted on the opposite arm and in a series of normal individuals, and in none did the exercise cause a rise of more than 10 mm. saline. These experiments show that the residual symptoms that follow occlusion of the axillary and subclavian veins are due to the abnormal venous pressure (Chart 1).

The severity of these symptoms depends upon the extent of the

development of the collateral circulation. In some, the collateral venous channels may become adequate to take care of the return blood, and there will be no residual symptoms. In others, there may be sufficient channels to care for the venous flow during rest, but not capable of coping with the increase in flow which follows exercise. In these the exercise causes an increase in the local venous pressure, retardation of flow and lowering of oxygen content. As long as the exercise is continued there is a gradual damming back

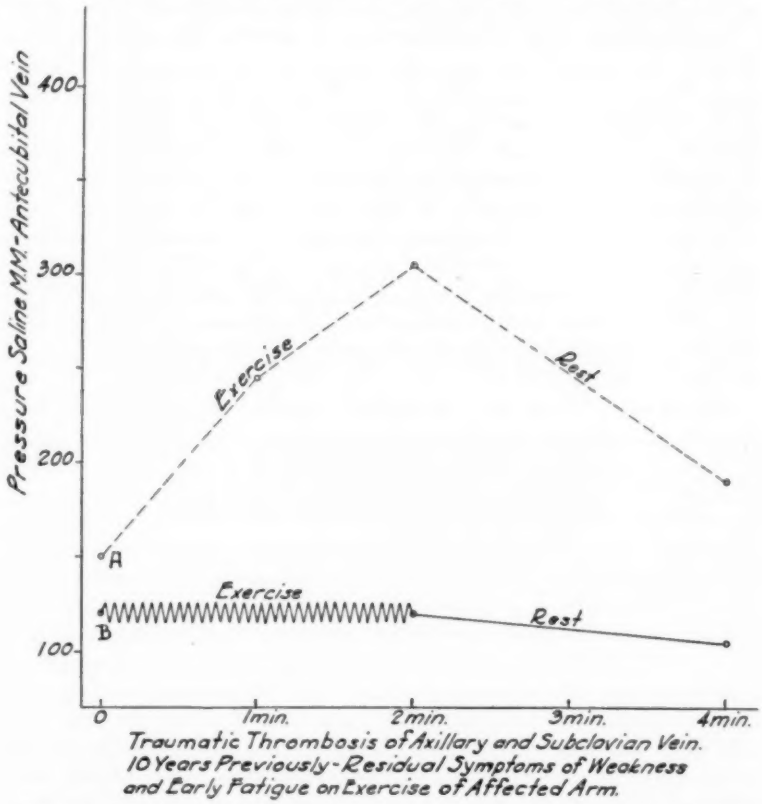

CHART 1.—Reaction of the local venous pressure to exercise in a case of permanent occlusion of the axillary and subclavian veins from phlebothrombosis—the post-thrombotic syndrome: *A*, Represents the venous pressure curve during exercise in the veins of the obstructed arm; *B*, The venous pressure curve, during exercise, in the veins of the normal arm.

of the venous blood under increasing pressure, thereby producing a sense of fatigue or weakness, pain, and finally edema. In still another group, even during rest, the venous pressure may be sufficiently high to cause persistent edema. In these, exercise, of course, elevates the pressure to an even higher level and causes an increase in the edema.

A presumptive diagnosis of axillary and subclavian vein occlusion can usually be made from an accurate history and careful physical examination. The diagnosis can be positively confirmed by means of venographs of the local venous circulation. We have previously described[14b] a simple method of directly visualizing the axillary and subclavian veins and will not repeat the technique in this communication. By such a method of study it is now possible to locate the point of obstruction, to demonstrate the extent of involvement and to visualize the remaining patent venous channels (Fig. 1).

A comparison of the venous pressure in the affected extremity with that in the normal arm provides additional information. In cases of swelling of the arm resulting from local venous obstruction, there is an elevation of the venous pressure in the involved arm, and normal in the opposite member. In cases of obstruction of the mediastinal veins there is an elevation of the venous pressure in both arms. In swellings of the arm not caused by venous obstruction, the venous pressure remains normal at rest and during exercise of the limb. Repeated venous pressure studies will also prove valuable in determining the progress in an individual case. Residual symptoms should be expected when the venous pressure remains elevated with the arm at rest, or shows an abnormal increase during exercise of the extremity.

Treatment. There are no known surgical measures that will completely relieve thrombosis of the axillary and subclavian veins. Surgical exploration has been undertaken in a few cases, but the end results do not seem to justify further attempts. In certain cases in which the thrombosis is extensive and in which there is an extreme degree of edema, multiple skin punctures may prove very helpful. This procedure must be done under strictly aseptic precaution. Thrombophlebitis and phlebothrombosis of the axillary and subclavian veins are best treated by complete rest, elevation of the extremity on soft pillows, and the local application of heat. Rest and elevation should continue until there is obvious development of collaterals. In practically all cases the edema will disappear within a few days to several weeks. There should be a gradual resumption of activities. The patient should be warned of the possible residual symptoms.

Thrombosis of the axillary and subclavian veins secondary to malignancies of the chest and axilla should be treated by rest and elevation of the arm. There is little hope of cure of the malignancy, but the effect of the local venous obstruction may be overcome to some degree by the formation of collaterals. The development of collateral venous circulation is a natural process. This process is retarded by conditions that increase the edema; it is aided by conditions that lessen venous congestion.

Summary. 1. The symptom complex of thrombosis of the axillary and subclavian veins is reviewed.

2. A classification and examples of the various types of thrombosis is given. Clinical studies from 17 cases are recorded.

3. The frequency of secondary thrombosis from malignancies of chest and axilla is emphasized.

4. The development of collateral circulation after occlusion of the axillary and subclavian veins is discussed.

5. An explanation of the post-thrombotic syndrome, based on the inadequate collateral circulation and elevation of the local venous pressure, is offered.

6. A résumé of treatment for the various forms of thrombosis is outlined.

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THE MYOCARDIAL DEGENERATION ASSOCIATED WITH UREMIA IN ADVANCED HYPERTENSIVE DISEASE AND CHRONIC GLOMERULAR NEPHRITIS.

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There occurs in uremia an unusual type of myocardial degeneration that apparently has escaped the attention of pathologists and clinicians. It is seldom seen in purely "obstructive" uremia, but contrariwise, it is not uncommon in those patients who exhibit renal insufficiency associated with severe hypertensive disease. It has also been seen in some patients with chronic glomerular nephritis. This myocardiopathy* is probably an important factor in the cardiac failure of uremia, a failure which we believe is rather frequent but often obscured by other aspects of the toxemia.

There are few references concerning the influence of uremia on the myocardium. Wood and White[12] reported on the electrocardiographic changes, directing attention to the existence of "toxic"

* "Myocardiopathy" is used here in lieu of a more specific nomenclature that necessarily awaits a detailed knowledge of these unusual myocardial lesions.

effects that could not be ascribed to digitalis therapy or to common types of myocardial degeneration. Heitz[5] and Chalier and Contamin[2] pointed out the frequency of pulsus alternans. Fishberg,[4] quoting these observations and certain personal experiences, believes that heart muscle may be directly injured by uremic toxemia. Only one report, as far as we know, deals with pathologic changes in the myocardium presumably due to uremia. Lüscher[7] described a severe interstitial hemorrhagic myocarditis in a nephritic patient, which was histologically identical with idiopathic interstitial myocarditis (Fiebach,[3] Sellentin[11]).

The lesions herein described are different from those ordinarily seen with heart disease. They were found in 34 uremic and preuremic patients whose clinical course and necropsy findings form the basis of this report.

Aside from hypertrophy of the heart, there is often in uremia a flesh-colored mottling of the muscle, usually most marked in the posterior and lateral walls of the left ventricle (Fig. 1). Section reveals yellowish-gray, buff, or occasionally pale salmon-colored foci of myocardial degeneration, usually having a uniformly smooth appearance. The cut surface is rather dry and slightly swollen, suggestive of some form of coagulation necrosis. A resemblance to firm suet may be noted. These foci vary greatly in size and shape, some being of millet-seed size, others so large as to occupy as much as one-half or more of the thickness of the ventricular wall (Fig. 2). In many instances they are fairly well demarcated, sometimes appearing as wedge-shaped lesions extending down from the epicardium into well-preserved myocardium. Often, however, this demarcation is indistinct, the lesions gradually merging with widespread degenerative changes of a similar nature, only less pronounced. The more striking color changes of acute myocardial infarction are not present, nor is any focal softening, mural thrombus, or any gross fibroblastic reaction demonstrable. These peculiar lesions of uremia apparently show a preference for the outer (subepicardial) zone of the posterior and lateral walls of the left ventricle (Fig. 3). They often collect under the epicardium, through which, in the absence of pericarditis, they are easily seen. However, they may be found in any part of the heart, *e. g.*, in the papillary muscles, and are often scattered irregularly in the walls of the right ventricle and auricle. In two instances we noted marked degenerative changes in the area of the sino-auricular node which were probably the basis for interesting electrocardiographic changes. The left auricle is not involved as often as other areas.

The overlying epicardium often shows a hyperemia which occasionally is so intense as to give a scarlatiniform appearance to the heart (Fig. 1). With changes of such degree the normal epicardial sheen may be lost, suggesting an oncoming pericarditis. The myocardial lesions on the freshly cut surface often become temporarily

more pronounced. Their color quickly fades in fixative solutions containing formalin, as does the color of all of the myocardium in cases of uremia. (Klotz No. I solution, frequently renewed, is a fairly satisfactory preservative.)

The above description applies to focal lesions easily recognized in most instances because of their location and their appearance. However, many hearts from uremic patients who had signs of cardiac failure did not show these lesions. Instead, the hypertrophied myocardium, which in the hypertensive state is usually firm and beefy red, was pallid, sometimes pale red or yellow-gray, and while generally firm, its cut surface had a swollen greasy appearance. The fascicular markings of the cut surface were usually lost. This degeneration was in some instances limited to a rather broad belt of muscle beneath the epicardium, suggestively confining itself to a particular layer of the myocardium. The papillary muscles in such instances were often concurrently involved. In other cases, the entire wall of large portions of the left ventricle showed the greasy pallor, the swollen cut surface and loss of fine muscle markings noted above. Occasionally, in such widespread degenerative changes a more intense focal subepicardial involvement could still be traced. We believe that these widespread changes are identical with the focal lesions described above, differing only in scope and severity.

Association of Pericarditis With Uremic Myocardiopathy. In 7 of the 34 cases gross pericarditis was present. In 6 instances it was of the typical uremic type, the exudate consisting of a thin deposit of glistening "frosty" fibrin, easily removed from an almost smooth but hyperemic epicardial surface. In the seventh case, a 14-year-old girl with chronic glomerular nephritis, the pericardial reaction was older (subchronic), with widespread adhesion. More common than grossly demonstrable pericarditis was a variable degree of hyperemia usually over those areas where the myocardial lesions were most pronounced. Its occasionally intense red appearance has been mentioned above. Uremic pericarditis was not seen in the absence of myocardial degeneration whether the latter was focal or of the diffuse type. It is therefore our impression that pericarditis is in most instances a complication of the myocardiopathy, probably a result of the same "toxic" process.

Histopathologic Changes in Uremic Myocardiopathy. The histological picture is usually less striking than the gross changes would indicate. The microscopist, mindful of the well-demarcated gross lesion that suggested focal necrosis, will be disappointed in finding merely a vacuolization due to fatty degeneration (Fig. 4), or else a hazy swelling of myocardial fiber (Fig. 5), or both of these changes. However, closer inspection indicates that this fatty degeneration differs from other types of such degeneration. The tendency to subepicardial rather than subendocardial localization as seen in

"tabby cat" or tigroid fatty degeneration is interesting. It should be noted, of course, that this subepicardial localization is relative and not absolute; the degeneration may be seen throughout. Possibly similar subepicardial degenerative changes are seen in other disease states, especially in association with pericarditis, but they are not so striking. The fatty vacuolization in uremic myocardial degeneration is usually very fine. It may be so small as to escape notice in routine examination, or it may be difficult to differentiate from hydropic vacuolization. Fat staining with Sudan III often yields a very fine red stippling, as if Cayenne pepper had been dusted over the section (Figs. 6 and 7). In advanced degenerations larger droplets of fat are also numerous, but seldom is the vacuolization as marked as in pernicious anemia or in the degenerations of some infections (diphtheria, occasionally acute rheumatic fever). In some instances the vacuolization gives a very fine moth-eaten appearance to each fiber (Fig. 4).

Other histologic features are hyaline degeneration and a tendency to marked swelling of the muscle fibers. The latter are often so increased in size as to diminish greatly the interstitial space in many

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LEGENDS FOR FIGS. 1 TO 11.

FIG. 1.—Uremic myocardiopathy; flesh colored subepicardial foci of myocardial degeneration (*X*), distinct from the epicardial fat (*Y*). Note congestion (dark) of the adjacent epicardium. Insert at lower corner shows tangential section through mottled areas. From a patient, aged 46 years, with cardiac failure and uremia. (Photography by Gosner, Philadelphia General Hospital.)

FIG. 2.—Advanced uremic myocardiopathy without pericarditis; tangential section, left ventricular wall. Malignant hypertension, cardiac failure, moderate azotemia.

FIG. 3.—Uremic myocardiopathy; note subepicardial localization, marked congestion in overlying pericardium and early pericarditis. Woman, aged 63, with paroxysmal dyspnea and ankle edema of 3 weeks' duration; B.U.N. 230 mg. per 100 cc. (Courtesy of S. Bellet and T. M. McMillan.[1])

FIG. 4.—Advanced fatty degeneration, uremic myocardiopathy. Note fine "moth-eaten" vacuolization. From focal subepicardial lesion (see Fig. 1.) (× 207.)

FIG. 5.—Swelling and foggy obscuration of myocardial fibers; early fatty degeneration; apparently earlier phase of degeneration (see Fig. 1). (×253.)

FIG. 6.—Fat stain (Sudan III) showing advanced fatty degeneration in a focal subepicardial lesion (see Figs. 1 and 4).

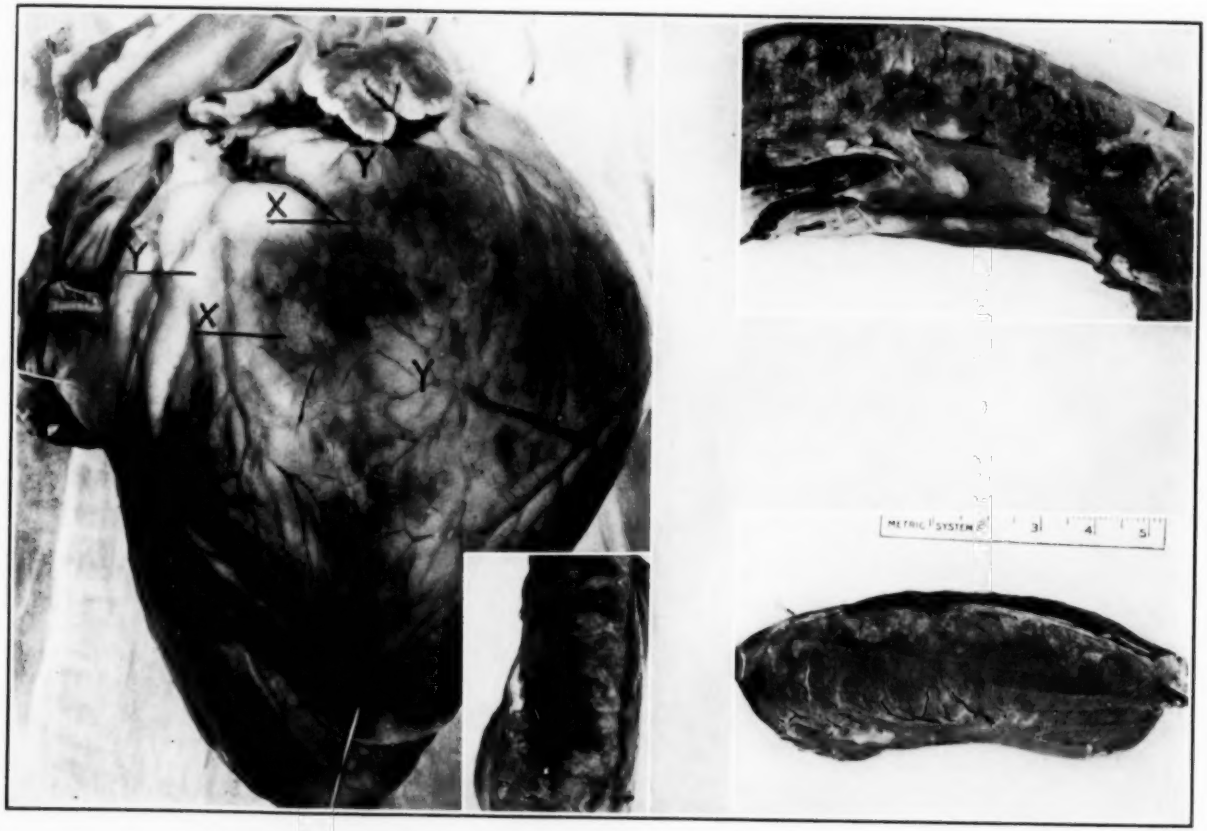
FIG. 7.—Diffuse fatty degeneration of the myocardium (common type) in uremia. Note fine but almost universal stippling (Sudan III).

FIG. 8.—Hyaline swelling and early fatty degeneration; transitional changes in same field (×207). Vines stain; man, aged 38 years, with blurred vision, vomiting, and blood pressure 284/176. Palpitation, moderate dyspnea, but no edema. *T* waves flattened in all three standard electrocardiogram leads. B.U.N. 150 to 220 mg. per 100 cc. Death in uremic coma.

FIG. 9.—Acute focal calcification, uremic myocardiopathy; a rare lesion. Note adjacent myocardial degeneration; man, aged 49 years, with dyspnea, hemoptysis, and malignant hypertension. B.U.N. 240 mg. per 100 cc.

FIG. 10.—Marked degeneration of the sino-auricular node in uremic myocardiopathy. *A*, The artery of the *S–A* node; *B*, normal auricular muscle. Arrows mark the border of the degenerated, poorly stained node. From a patient with uremia, cardiac failure, bradycardia, and nodal rhythm (×69).

FIG. 11.—Marked degeneration in the *S–A* node; the nodal fibers, normally small and irregularly disposed, are here so degenerated, diminished in size, and so poorly stained as to be barely visible. Note the hemorrhagic infiltration.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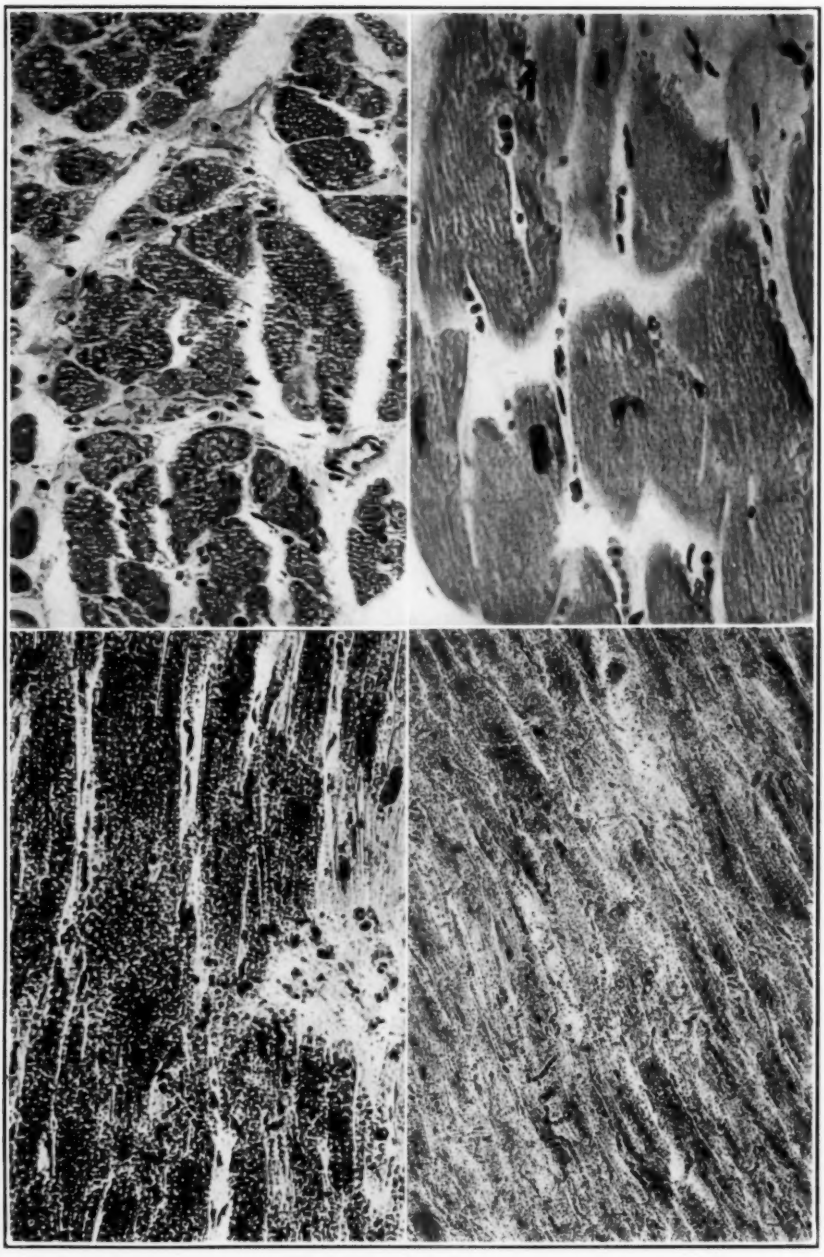

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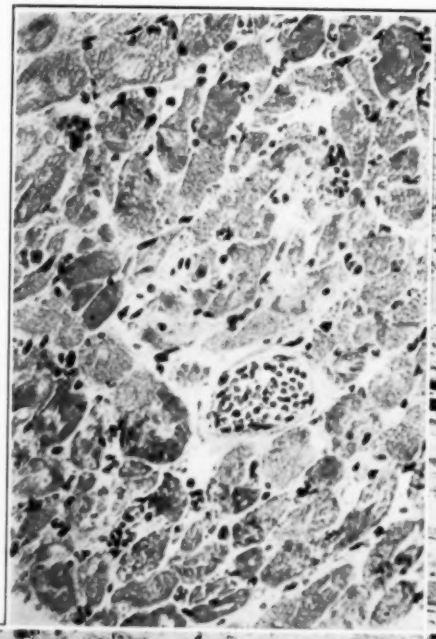

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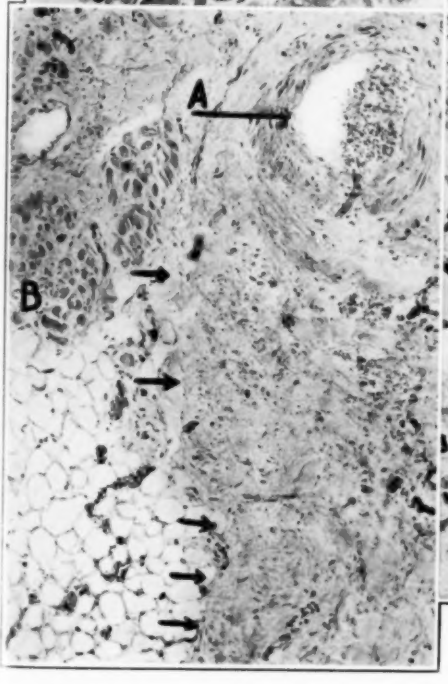

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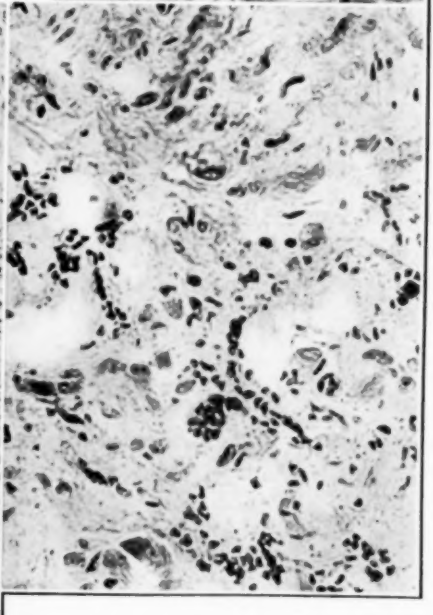

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areas (Fig. 5). This swelling exceeds any enlargement due primarily to cardiac hypertrophy. With it there is often a foggy obscuration so that sharpness of detail is lost, not only of striation, but even of the actual outline of the fibers. In this fogginess the swollen fiber may present some appearance of homogeneity suggestive of an acute hyalinization (Fig. 8). Some stains (Vines) show this to better advantage than the routine hematoxylin-eosin. These changes, hazy swelling and hyalinization, apparently precede the fatty degeneration, which in some instances was only slightly or moderately developed when death occurred. Occasionally most of the sarcoplasm has disappeared, the fibrillæ being small and broken and replaced by a myxomatous type of edema.

We have noted one instance of acute focal calcification in association with this myocardiopathy (Fig. 9). Fishberg[4] cited a case of chronic glomerulonephritis in a young woman whose myocardium was the site of focal calcification. These two interesting cases possibly have a similar pathogenesis.

There is usually little or no cellular infiltration. In some cases, scattered monocytes and an occasional neutrophil or eosinophil are noted. We have seen in only 2 instances in this series of 34 patients what might be termed a moderate degree of cellular infiltration. In conformity with standard nomenclature, the term "uremic myocarditis" would therefore not be truly acceptable.

The Coronary Arteries and Arterioles. The coronary arteries show a variable, occasionally considerable degree of atherosclerosis. This usually consists of discrete deposits of atheroma with yellow discoloration of the intimal surface. Advanced arteriosclerosis with fibrotic and calcareous degeneration leading to a serious degree of stenosis or actual occlusion of main coronary branches was seldom seen. In one instance, advanced stenosis of the right coronary artery was associated with a small organizing posterior myocardial infarction which was distinct in its appearance from the surrounding lesions of uremia. In practically all other cases the coronary arterial system appeared to be satisfactorily patulous and in many instances the arteries were not only surprisingly free of gross pathologic change, but were larger than normal, suggesting a compensatory increase of capacity in keeping with the cardiac hypertrophy.

Microscopy confirmed the usually good and often excellent gross appearance of the large arteries, but revealed a common incidence of arteriolar sclerosis. This, however, was uneven (segmental) and generally of mild degree. The usual findings were hyaline degeneration of the media and eccentric thickening of the intima seldom giving the impression of significant narrowing. Actual arteriolar necrosis (fibrinous necrosis), acute thrombotic closure and "onion-peel" hypertrophy of the media were not seen, although they were commonly present in the kidneys of the same patient. The capillaries were often distended, containing many erythrocytes. When

myocardial swelling was marked, the adjacent capillary bed was largely obliterated.

The Clinical Aspects of Uremic Myocardiopathy. This group of 34 patients, consisting of 17 men and 17 women, varied in age from 18 to 72 years; 21 were in the third, fourth and fifth decades, 9 in the sixth. There were 23 negroes and 11 whites. Our data are insufficient to be of value in tracing any familial tendency.

The large majority of these patients had severe hypertension. The systolic pressure generally was above 200 mm. mercury; the diastolic ranged from 120 to 140 and occasionally was as high as 180 mm. Eye-ground examination of 16 patients revealed in all a varying degree of the angiospastic and hemorrhagic changes of hypertensive disease. The age level, the high diastolic pressures, the rather rapid clinical course and the severe renal vascular damage that later was regularly found placed most of these patients in the classification of malignant hypertensive disease. Two of them were finally considered to be cases of chronic glomerular nephritis.

The patients could be separated into two groups: those with easily recognized heart failure, and those in whom the early presence of dyspnea was obscured by various complaints suggestive of toxemia, such as amblyopia, severe headache, vomiting, purpura and psychosis. In this latter group, the attending physician easily recognized the presence of uremia or of hypertensive encephalopathy. Dyspnea, which in many cases antedated the other symptoms, persisted and in some instances was accompanied by progressive edema, all of which was thought to be merely incidental to the progress of uremia. However, the patients in the first group were invariably regarded as victims of hypertensive cardiovascular disease with myocardial failure due to coronary arteriosclerosis. Dyspnea, palpitation, edema, gallop rhythm and bloody sputum were prominent features indicative of cardiac strain and decompensation. Other occasional signs and symptoms, possibly suggestive of uremia, assumed a secondary importance and the true clinical status was established only when laboratory reports revealed the presence of advanced renal insufficiency and serious azotemia. This state in which cardiac failure was the preponderant clinical feature lasted for a variable time, often for 2 or more weeks, and was prolonged in two instances for 3 months, the azotemia remaining at high levels. Usually there was an increasing mental dullness which finally ended in coma if life persisted long enough despite the circulatory failure. Often both advanced heart failure and coma were present in the terminal stage. Heart failure in the majority of cases was predominantly of the left ventricular type, death following extreme dyspnea and pulmonary edema. In others, failure gradually became generalized, accompanied by swollen liver, engorged neck veins and peripheral edema. Right heart failure was constantly predominant in only one patient. The hyperten-

sion persisted usually to almost the last day of life, regardless of the extent of circulatory failure. In a few there was a terminal drop, seldom, however, below 150 mm. systolic and 100 mm. diastolic. Arrhythmia was uncommon and no instance of systemic embolism was recorded. Two cases of left heart failure were complicated by pulmonary infarction, which could only be considered incidental to the intense passive hyperemia of the lungs.

Cardiac murmurs were fairly frequent, always systolic, and usually heard in both aortic and mitral areas. They were almost all functional, as revealed by necropsy, and could be ascribed to ventricular dilatation or anemia. Gallop rhythm was heard in 6 patients; it was of the ominous type—apical, presystolic, and associated with left ventricular enlargement. Pulsus alternans was either seldom recognized or else not present to the extent claimed by other observers.[2] Cardiac rates as high as 125 per minute were seen in some patients on admission to the hospital in the midst of acute left heart failure. They gradually were reduced as a result of bed rest and possibly digitalis therapy, and then usually remained between 70 and 100 despite the presence of dyspnea and increasing azotemia until shortly before death. There were 3 patients with bradycardia (rates, 52–65). Bradycardia has occasionally been noted in uremia.[6] While comparatively uncommon, the association is, we believe, authentic and is based, at least in some patients, on degenerative changes in the right auricle involving the sino-auricular node (Fig. 10). Wood and White[12] in their electrocardiographic study found 3 instances of sino-auricular block.

Laboratory Data. Urinalysis in practically every case showed low and fixed specific gravity coupled with a varying degree of albuminuria. In 28 patients the blood urea nitrogen was elevated above 60 mg. per 100 cc.; in most of these it ranged from 100 to 250 mg. per 100 cc. Of the 6 remaining patients, 2 died before blood chemistry studies were completed. Four patients who will be discussed later had only moderate azotemia, the blood urea nitrogen being 32 to 50 mg. per 100 cc. In 3 of these 4 patients, urea clearance tests pointed to renal insufficiency. Creatinin retention was present in each of 21 patients, ranging from 3 to 18.5 mg. per 100 cc.

The varying degree of anemia usually associated with uremia was noted in this group. Some erythrocyte counts were as low as 2,500,000, and in one instance, 1,800,000. The majority of patients had 3,500,000 or more; a few had close to 5,000,000 erythrocytes; but in such instances vomiting and hemoconcentration were possibly important factors.

The degree of acidosis likewise varied greatly. The CO_2 combining power was determined in only 7 patients, of whom 3 showed no diminution, 2 a moderate diminution, and 2 a marked acidosis (17 vol. %).

The Wassermann reaction was positive in 5 patients. It appeared to be an incidental finding, since no clinical or pathologic evidence of syphilis was found in any case.

Electrocardiographic Studies. In 18 patients there were 12 instances of left axis deviation. Arrhythmia was relatively uncommon; 1 patient had nodal rhythm; 2 others with bradycardia were not studied electrocardiographically. One patient developed auricular fibrillation and 3 instances of ventricular extrasystoles were noted.

T-wave changes and deviations of *ST* intervals from the isoelectric line were common. Flattening or inversion of *T*1 and *T*2 in combination was noted 6 times; of *T*2 and *T*3, once; of all 3 *T* waves (indirect leads), 4 times. Depression of *ST* in Leads 1 and 2, twice; of *ST*2 alone, 4 times. The chest leads showed no unusual changes in the absence of pericarditis.

Occasional Findings. Large *S* wave in Lead 2 and also prolongation of *QT*, twice; the latter has been noted in connection with hypocalcemia common in uremia.

Thus numerous deviations from the normal electrocardiographic pattern were noted. Undoubtedly some of them were due to uremia, as suggested by Wood and White.[12] We believe, however, that only a detailed analysis beyond the scope of this report can estimate the significance of the electrocardiographic changes. Many factors are involved; for example, Bellet and McMillan[1] have demonstrated that some of these changes are due to pericarditis.

Dyspnea, Edema and Absence of Angina Pectoris. Certain clinical features are worthy of further comment. Dyspnea was present in every case, usually from the beginning. Many patients were incapacitated by paroxysmal dyspnea, while others became aware of a very slowly developing shortness of breath that continued for many weeks, occasionally for as long as 3 or 4 months. In some instances, a respiratory infection appeared to initiate this subtle cardiac failure. Dyspnea was undoubtedly aggravated by the acidosis common in uremia, but its cardiac origin nevertheless was clearly evident in the history and concomitant physical signs in every case. It did not differ, except terminally, from the dyspnea seen in other types of heart disease.

Edema developed in the majority of these cases, but it was variable in degree and in the time of its appearance. While many patients eventually became markedly edematous, others developed only a moderate degree of ankle edema shortly before death and occasionally edema was conspicuously absent. Pulmonary edema was, of course, usually present. In some patients, not only the absence of peripheral edema, but actual dehydration was striking, contrasting with evident cardiac decompensation as indicated by recurring pulmonary edema, gallop rhythm, and a moderate venous hypertension. Possibly polyuria secondary to renal tubular atrophy

is a determining factor in the relatively "dry" type of heart failure seen in some uremic patients.

In contrast to the constant presence of dyspnea and the appearance in the majority of some degree of edema, angina pectoris and precordial pain were absent in all but 2 uncomplicated cases. Chest pain occurred with the onset of pericarditis and also appeared in the history of 2 patients who at necropsy had no structural basis for it except cardiac hypertrophy and uremic myocardiopathy. The common absence of an anginal syndrome is interesting when one considers the usual degree of ventricular hypertrophy and the persistently severe hypertension in these cases. Sensitivity to pain is probably diminished in uremia. Nevertheless, pain was present in 4 of the 6 patients with acute pericarditis, a complication that occurs usually near the end of life when mental impairment is evident. The absence of serious occlusive coronary artery disease may be of some importance in this picture of painless myocardiopathy.

Abstracts of the clinical findings in 2 patients are herewith presented:

Case Reports. Case 1.—C. M., negro male, aged 45, was admitted to the Philadelphia General Hospital (service of Dr. F. J. Kalteyer) complaining of shortness of breath and cough. In July, 1937, he became weak, short of breath, and began to cough with blood-streaked sputum. No chest pain was felt, but recently he was conscious of rapid heart action and palpitation. Past medical history was irrelevant. Examination revealed a mentally confused, dyspneic negro, with cardiac enlargement, râles at both lung bases, distended neck veins, and enlarged liver. The blood pressure was 225 mm. systolic, 155 diastolic. The B.U.N. varied between 110 and 140 mg. per 100 cc. CO_2 was 62 vol. %. Red blood cell count was 3,500,000. Digitalis therapy and intravenous sucrose injections were of no value. The patient developed Cheyne-Stokes respiration, and after lapsing into coma, died on Oct. 8, 1937.

Case 2.—A. P., a colored woman, aged 53, was admitted to the Philadelphia General Hospital (service of Dr. Robt. Torrey), July 3, 1937, complaining of shortness of breath which, while present in mild degree for possibly a year, became very marked in the last 5 weeks. It was accompanied by leg edema, but there was no precordial pain. The amount of urine was progressively less in recent days.

Examination revealed an obese woman with Cheyne-Stokes respiration. Eye-ground examination showed advanced "albuminuric" retinitis. The blood pressure was 220/110, the neck veins were prominent, and a few râles were heard at both bases. The heart was enlarged to the left and a presystolic gallop rhythm was heard in the apical area. Occasional extrasystoles were heard, but the cardiac rhythm was otherwise normal, rate 80 per minute. The liver was slightly enlarged and there was moderate leg edema. On July 6, convulsive seizures suggestive of hypertensive encephalopathy occurred, during which severe pulmonary edema developed, terminated finally by death. Laboratory examination for determination of azotemia had not been completed, but necropsy revealed typical lesions of necrotizing arteriolar nephrosclerosis and uremic myocardiopathy. The coronary arteries, slightly atheromatous, were widely patent, actually enlarged throughout.

Discussion. While small focal lesions, possibly similar in type to those herein described, are occasionally found in hearts of non-hypertensive individuals, the well-developed gross changes represent, we believe, a myocardial degeneration characteristic of malignant hypertensive disease or of chronic glomerular nephritis in which uremic or pre-uremic states have been reached. We have included the term "pre-uremic" because, while the large majority of these patients had marked azotemia, 4 of them showed it only to a moderate degree. Of the latter, 1 patient had left heart failure for 2 months, associated with persistently high blood pressure, and a blood urea nitrogen level of 42 mg. per 100 cc. Necropsy revealed the myocardial degeneration of uremia and the renal lesion of malignant nephrosclerosis. A second case died with hypertensive encephalopathy, complicated, however, by left ventricular failure. The third case, a woman, aged forty-eight years, with marked diastolic hypertension, was hospitalized with left heart failure. The existence of advanced renal sclerosis was considered likely on the basis of the eye-ground changes and the fixed low specific gravity of the urine. However, the blood urea nitrogen was only 34 mg. per 100 cc. While under observation, the patient developed hypertensive encephalopathy. Later, both the cardiac and mental states improved with the concurrent disappearance of the moderate azotemia. Within 6 weeks, cardiac failure of the "dry type" and encephalopathy recurred, associated with a rise in blood urea nitrogen to 32 mg. per 100 cc. Death followed recurring paroxysmal dyspnea and pulmonary edema. Necropsy revealed the typical uremic myocardiopathy and brain changes that are associated with hypertensive encephalopathy.[9] In the fourth case, azotemia had apparently receded from a higher level, yet clinically there was increasing evidence of cardiac decompensation and toxemia. At necropsy, the myocardial damage was extensive. It thus appears that the myocardial changes are not absolutely dependent on the presence of severe azotemia, although most often are seen with it. Rather, they suggest a "toxic" effect in the hearts of some hypertensive patients who suffer from a progressive poisoning which culminates in uremia. This course is sometimes interrupted by the development of encephalopathy.

The myocardiopathy is in our experience a common occurrence. We have no exact figures but believe it can be seen in the majority of the uremic patients who exhibit signs of heart failure, other than the immediately terminal failure commonly seen in the last few hours of life. The high incidence in negro patients is due to the comparatively large colored population at the Philadelphia General Hospital, and the greater frequency of severe hypertensive disease in the negro race.[8,10]

The pathogenesis of this degeneration is undetermined. The

importance of anoxemia has been emphasized in many circulatory disease states and two conditions favor its development in hypertensive and renal disease, namely, arteriolar sclerosis and anemia. Myocardial arteriolar sclerosis was often present, but its nonnecrotizing character has been noted by others as well as ourselves.[4] The possibility of arteriolar spasm cannot be ignored. However, the absence of ischemic necrosis and of widespread fibrotic replacement suggests that this myocardial degeneration is not entirely due to occlusive vascular disease. Moreover, such degeneration has not been seen in advanced emphysema, in chronic coronary artery insufficiency, or in cases of syphilitic aortitis complicated by almost complete stenosis of the orifices of the coronary arteries, examples of cardiac involvement in which anoxemia supposedly plays an important rôle. Finally, in this connection, the slight incidence of angina pectoris should not be forgotten. We believe that anoxemia is at the most only a contributing factor.

The degree of anemia varied greatly and thus no definite conclusion could be drawn as to its importance. Pallor of the myocardium is generally present with marked anemia; yet often, the diffuse as well as the focal uremic degeneration was present in patients with erythrocyte counts above 3,500,000. The same lack of parallelism was seen in reference to acidosis. While these factors cannot be disregarded, none of them can be accepted on the basis of the accumulated data as the major cause of the myocardiopathy. We believe that the lesions are a result of the action of a "toxin," the nature of which is part of the secret of uremia.

Summary. A peculiar type of myocardial degeneration appears to be intimately associated with the uremic and pre-uremic states of arteriolar nephrosclerosis and chronic glomerular nephritis. It is found especially in those patients who have cardiac failure. The latter may be the outstanding feature of uremic intoxication. Pericarditis may be regarded as a complication of this myocardiopathy.

We are indebted to the chiefs of service, both medical and laboratory, for the privilege of utilizing the clinical and pathologic material at the Philadelphia General Hospital in the preparation of this report.

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THE RELATIONSHIP OF MIGRAINE TO HYPERTENSION AND TO HYPERTENSION HEADACHES.

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The majority of patients who have hypertension are subject to headache at one time or another and frequently it is the initial complaint. In 1913, Janeway[1] observed that his patients who had hypertension complained of headache as their most frequent symptom. He found that evaluation of the rôle that hypertension played in producing these headaches was difficult, as a large number of these patients had been subject also to migraine at some time during their lives. In recent years, those who have been interested in hypertension have likewise noted its frequent association with migraine. These observations have been made casually and as far as we know, a previous attempt has not been made to establish such a correlation statistically. It is for this purpose that the present study was undertaken.

The characteristic features of a migraine headache are the periodic nature of the attacks of pain that are confined to one side of the head (hemicrania) and associated visual disturbances, especially scotomas, and nausea and vomiting. There may be a wide variation from the typical description although the more the symptoms vary from the classic symptoms the less likely is the headache to be a true migraine. Some common variations observed are the absence of hemicranial limitation of the pain and the absence or minimal nature of the visual and gastric disturbances. In almost all cases of true migraine, however, the patient will have had one or several attacks, at one time or another, that are associated with visual and gastro-intestinal disturbances. The attack may last from one to several hours or days.

The headache usually considered to be most frequently associated with hypertension is the so-called typical hypertension headache; that is, one which is present when the patient awakens, or which awakens him during the early morning hours. It reaches its greatest intensity before breakfast and disappears after breakfast or during the early morning. The headache is usually occipital but may occur in any part of the head. Seldom is it unilateral. It may vary from a dull ache or feeling of pressure to a severe bursting or throbbing pain. Visual, auditory or other aura may precede the headache and nausea and vomiting may accompany it, thus giving some resemblance to migraine. However, these phenomena are rare.

Method of Study. One hundred patients who had been seen in consultation at the clinic because of hypertension were carefully questioned by us as to the presence of migraine or a previous history of migraine. These patients were seen consecutively and no attempt was made to select them. All had a systolic blood pressure of more than 160 mm. of mercury and most of them had one or more symptoms usually associated with hypertension. We also noted the presence of other types of headache and the change, if any, that had occurred in the migraine headache, if such had been present before the hypertension was discovered. All patients were questioned as to the family history of both migraine and hypertension. The age of the patients varied from 20 to 65 years; the large majority falling between the ages of 40 and 60 years. There were 38 men and 62 women.

In order to have a control series to compare with the group of cases of hypertension, a second study was made on a series of 100 patients who had normal blood pressure. These patients were selected at random from routine admissions to the clinic. The same care was exercised in eliciting a history of migraine from the patients of this group. The ages of these patients were between 40 and 60 years. Sixty of the group were women and 40 were men. The general preponderance as to age and sex thus compared favorably with those of the hypertension group.

Result of Study. *The Association of Migraine with Hypertension.* A surprisingly large number (79%) of the group of patients who had hypertension admitted either that they were subject to migraine at present or had had such attacks in the past. In the control group there was an incidence of migraine of only 15%. This compares closely with an incidence of migraine of 18% as found by Traut and Vrtiak[2] in their control group in a study of allergy in cases of arthritis. Fifty-six patients, a majority of those seen, indicated that they were still troubled with migraine to a variable degree despite the onset of hypertension. The presence of hypertension had been accompanied by no change in the symptoms of migraine of 31 patients; the number and severity of the attacks of migraine had decreased in 17 and had become accentuated in 8 cases.

It is interesting to note that in the total registration at the clinic during 1938, the diagnosis of migraine was recorded approximately 5 times as frequently in the group in which a diagnosis of hypertension was also recorded as in the group in which the diagnosis of hypertension was not recorded. The incidence was 7.7% and 1.6%, respectively.

The Association of Migraine with Hypertension Headaches. As has been previously stated, it is known that many patients who have a high blood pressure experience the development of the so-called hypertension type of headache. Of the 100 patients who had hypertension and who were studied, 44 complained of a hypertension type of headache. Of the 79 patients who had migraine, 38 (48%) experienced the development of a hypertension type of headache also, but of the 21 patients who had not had migraine, only 6 (28%) experienced the development of a hypertension type of headache.

Twenty-three of the 79 patients who had related a history of migraine were troubled no longer with this complaint at the time

when they had hypertension. Seventeen (69%) of these, however, had experienced the development of the hypertension type of headache. Of the 56 patients whose migraine persisted after the onset of hypertension, 21 (37%) also had experienced the development of a hypertensive type of headache, thus having attacks of headache characteristic of both disease processes.

Incidence of Family History of Migraine and Hypertension. Only 23% of the group of patients who had hypertension gave no family history of migraine or hypertension. Of the 79 patients who had associated migraine, 37 (approximately 46%) gave a history of migraine in their respective families, and of the 100 patients who had hypertension, 67% gave a family history of hypertension and 43% gave a family history of both migraine and hypertension. Of the 21 cases in which no migraine was associated, only 2 (approximately 10%) gave a history of both migraine and hypertension. Thus, it would seem that the association of migraine and hypertension is intimately concerned with hereditary factors common to both conditions.

Relationship of Age and Sex to Migraine and Hypertension Headaches. The incidence of migraine was approximately the same in both men and women. Approximately 40% of the 42 patients who had hypertension and who were more than 45 years of age no longer had migraine as compared with only 17% of the 37 patients who were less than 45 years of age. This would indicate that age, rather than the onset of hypertension, was the factor in the relief of the migraine. It is interesting that of the group of patients who had migraine, the men were much more likely to experience the development of hypertension headaches than the women by a ratio of about 2:1.

Comment. One cannot follow a number of patients who have hypertension without being impressed by the frequency with which migraine or the history of previous migraine occurs in association with hypertension. That this clinical impression is well founded is borne out in this study in which it was observed that migraine occurred approximately 5 times as frequently among patients who have hypertension as it does among individuals who do not have hypertension. The remarkable frequency of this association cannot be overlooked. On the other hand, the significance of such a relationship is not readily apparent. It is probable that a common factor in the pathogenesis of the two conditions is intimately concerned with their close association. The importance of a vascular factor in the production of attacks of migraine is now well known and there is considerable evidence that vasoconstriction plays an important rôle in producing the attack of migraine as it does in the production of hypertension. The common factor in the two conditions may be influenced by genetic factors which particularly concern the inheritance of a certain type of personality. Wolff's[3]

characterization of the person who has migraine as a person who has unusual ambition, who is meticulous and exacting, and who is a hard driver with the ability to accomplish much in a short time is certainly typical also of the personality of the patient who has hypertension. The close association of migraine with the development of a hypertension headache is also noteworthy. A certain number of patients studied were noted to have recovered from attacks of migraine before or at the time of onset of their hypertension. It seems unlikely that the onset of hypertension was the cause of the cessation of migraine, in view of the fact that a greater number of individuals retained symptoms of migraine in spite of the presence of hypertension. Some of these, moreover, were found to have experienced the development of hypertensive headaches and some were prone to have attacks of either type. Finally, our results tend to indicate that of all individuals who experience the development of high blood pressure, those who previously had had migraine are more likely to experience a hypertensive type of headache as one symptom of the hypertension than those not so afflicted.

Summary. Migraine occurs approximately 5 times as often in a group of patients who have hypertension as in a group of non-hypertensive patients of corresponding ages. The association of migraine with hypertension is probably influenced by genetic factors. Some patients experience a cessation of attacks of migraine prior to or coincident with the development of high blood pressure. This seems to be related more to the advancing age of the patient than to the onset of hypertension. Individuals who no longer have migraine headaches frequently experience those of the hypertension type. Those who retain their migraine are likely to have both types severely. An individual who has migraine is more likely to experience the hypertension type of headache than one not similarly afflicted.

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DIABETIC CONTROL VERSUS CALORIC SUFFICIENCY IN THE TREATMENT OF DIABETES AND PULMONARY TUBERCULOSIS.

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The peculiar susceptibility of the diabetic to tuberculosis has excited the interest of clinicians for hundreds of years. Indeed, Areteus not only gave a clear and comprehensive description of

pulmonary tuberculosis, but also defined and described diabetes mellitus in the second century, A.D.

Primary infection depends upon contact, and is no more frequent in diabetics than in non-diabetics. This is clearly indicated by skin tests in young diabetics. It is the loss of resistance to tuberculous infection which follows the development and lack of control of diabetes, which accounts for the high incidence of tuberculosis. Among the questions which have puzzled students of the disease, has been the problem whether or not the limitation in total number of calories prescribed by the physician or taken by the patient has in itself exerted a definite influence upon the development and course of pulmonary tuberculosis. It is with special reference to this question that an attempt is made to review certain features in the association of the two diseases that have come to my attention since 1920 through the analysis of 396 cases.*

Incidence of Tuberculosis Among Diabetic Patients in Different Countries and Different Problems of Treatment. If the limitation of calories for diabetic patients is of significance in producing pulmonary tuberculosis, then it follows that one should be able to show differences in the incidence of pulmonary tuberculosis among the diabetic patients of this series in accordance with the differences in practice in three different periods. Thus, between 1898 and 1914 the attempt to treat diabetes mellitus was conditioned by the doctrine that, although the sugar and carbohydrate in the diet should be restricted, the amount of protein and fat consumed should be kept as high as possible in the attempt to prevent loss of weight. It was not until 1914 when undernutrition as a fundamental method of treatment in order to control diabetes was introduced that actual weighing of the food and limitation of the calories was used at the Deaconess Hospital. That period from 1914 to 1922 was a period when the caloric prescriptions were greatly restricted and, indeed, it was by no means uncommon, for patients to leave the hospital with a total dietary prescription of from 900 to 1200 or 1300 calories. Since 1922, however, although the weighing of food has continued to be prescribed, no such limitation of calories has been followed, and indeed the prescribed calories per kilogram of body weight of the patients has varied from 30 to 50 or 60 calories per kg., depending upon the age and condition of the patient.

The incidence of pulmonary tuberculosis among 3575 diabetic patients at death was as follows: from 1897 to 1914, tuberculosis caused 4.9% of 325 deaths; from June, 1914, to August, 1922, 4.9% of 835 deaths; from 1922 to 1929, 5.5% of 1434 deaths. Finally, in the late insulin era, from January 1, 1930 to 1935, tuberculosis caused 4.8% of 981 deaths. Therefore, as observed in our

* I am fortunate in having available both the autopsy data at this hospital and the follow-up data of some 15,000 diabetic patients from 1898, when Dr. Joslin began practice.

series, there was no significant variation in the percentage of deaths from pulmonary tuberculosis during the period of maximum treatment with undernutrition.

A better method of analysis is an expression of the death rate from tuberculosis in relation to the total years of diabetic life, as shown in the following table:*

YEARS OF LIFE EXPOSED, TUBERCULOSIS DEATHS AND DEATH RATES IN SPECIFIED PERIODS.

	Years exposed	Expected tuberculosis deaths	Tuberculosis death rate per 1,000
1897 to 1913	1,551	17	11.0
1914 to August 6, 1922	5,368	61	11.3
August 7, 1922 to 1928	18,027	74	4.1

The decrease in tuberculosis during the insulin era from a rate of 11.3 to 4.1 is clearly evident.

In the period 1898 to June, 1914, the average duration of diabetes to death was 4.8 years of 331 fatal cases in a total of 1588 years of diabetes. Of these cases, 19 died of tuberculosis, or 1 case per 83.6 years of diabetic life. Between June, 1914, and August 1, 1922, the average duration of diabetes to death was 6 years for 597 cases, a total of 3582 years of diabetic life, and there were 47 cases of tuberculosis (1 case in 76 years of diabetic life). Between 1922 and 1930, among 1401 fatal cases with total years of 11,441.2 of diabetic life, there were 87 cases of tuberculosis. Thus, the incidence has fallen to 1 case in 131 years of diabetic life. In the first two periods, then, characterized first by overfeeding and then by underfeeding approximately the same incidence of tuberculosis occurred. Improvement in the rate occurred during the last period when better control of the diabetes was brought about, chiefly through the use of insulin. Indeed, we may expect still further surprises in our tuberculosis statistics. In the last 3 years (ending Jan. 1, 1940) no case has occurred in a diabetic under 20 years of age.

Furthermore, if we can compare the incidence of pulmonary tuberculosis in American clinics exemplified by this hospital, with the incidence among diabetic patients whose later course has been carefully followed up in the European centers, quite a different picture is presented. In Labbè's[7] large hospital clinic in Paris, pulmonary tuberculosis caused 40% of the deaths in 1930, 1931 and 1932. Ponteva[4] reports a follow-up of 86 patients with diabetes treated before insulin and 645 patients treated since the introduction of insulin in Finland; pulmonary tuberculosis caused 18.8% of the total deaths in their follow-up. Bertram,[1] in Hamburg, reported that 80% of his cases of diabetes mellitus who had had diabetic coma subsequently developed pulmonary tuberculosis. Himsworth,[3] in an analysis of 230 consecutive diabetics upon their

* I am indebted to Mr. Herbert H. Marks of the Metropolitan Life Insurance Company for the tabulation of these data.

first hospital visit in London, found 15 cases of tuberculosis. These figures from foreign countries are cited since in each instance it is fair to state that the restriction of total calories in the diet by means of weighed diet is not carried on so rigidly as in the series used for comparison. It is evident, therefore, that the incidence of pulmonary tuberculosis among diabetic patients is much greater among patients treated with less rigid dietary control.

In our series of 396 cases, the usual etiologic factors for pulmonary tuberculosis were sought. Contact with open pulmonary tuberculosis was a necessary and prominent feature, but as you will see later, unquestionably nutritional and constitutional factors are of great importance.

Unfortunately, pathologic data bearing on our problem are conspicuously few. At this hospital we have only had 17 autopsies performed upon tuberculous patients in about 360 autopsies. The descriptions of the findings in autopsies upon diabetic patients with tuberculosis in the literature are in most instances not very detailed. Nevertheless, it is true that one finds in diabetic patients tuberculosis in all stages and showing no unusual tendency to caseation, cavitation or site of lesion.

Metabolic Features Favoring Development of Tuberculosis in the Diabetic. In this series the following facts were outstanding: 1, 83% of the cases developed active tuberculosis after the onset of diabetes. 2, Tuberculosis of adult type occurred more than 12 times as frequently in patients whose diabetes began in childhood than in Massachusetts school children followed up in State clinics. 3, Between 1923 and 1929 pulmonary tuberculosis developed in 8% of 105 diabetic patients within 3 years of recovery from coma. Among 97 patients treated for coma between February, 1929, and November, 1932, 24 died of other causes within a year or two. Of the 73 remaining patients, 13 have developed tuberculosis within 5 years. So far as I know, no other metabolic disorder or no other clinical condition can be predicted to result in pulmonary tuberculosis in almost 20% of the cases within 5 years. Considering the subject from the other angle, when we reviewed the 396 cases, almost 20% were known to have had diabetic coma before we saw them or at some other hospital or under family physicians at home. Although we cannot get reliable data for the entire series and particularly for the entire period, it is very likely from an analysis of the course and symptoms that the incidence of severe acidosis, even though it did not reach the stage of full coma, was probably close to 50% in this series. The existence of coma does not necessarily mean that the diabetes is fundamentally severe diabetes. In fact, quite the reverse is often the case. A young woman who required 1100 units of insulin in 11 hours to bring her blood sugar from 1100 to 200 mg. per 100 cc. recovered from her coma, in which she had been anuric and pulseless, finally left the hospital with such mild diabetes that she did not need insulin at all. The existence

of coma is primarily evidence of gross lack of control and overconsumption of the patient's stores of food by reason of complications such as fever or infection. 4, Great loss of weight has been a striking feature of the patients. Actually, however, when we come to analyze this series, this fact may not be used as an argument in support of the idea that the prescription of limited calories was of itself an etiologic factor. Somewhat to my surprise, I found that in those patients who had lost from 30 to 50 pounds in weight (and actually in 219 cases the average loss of weight was 42 pounds, and loss of weight in excess of 75 pounds occurred in 19 cases) that these losses of weight occurred during periods when the diabetes had been uncontrolled. That is, the losses of weight occurred during those first months or first years of the diabetes, when in many instances the diabetes was not even discovered and when the patient, to use his own statement, was "eating his head off."

For an understanding of the effects of these metabolic disturbances we may turn to the conditions possibly favoring the growth of the tubercle bacillus.

Lipid Content of Diabetic Lungs. One of the most characteristic features of diabetic tissues is the remarkable alteration of the fat content of certain organs, namely, the liver, spleen, arteries and nerve tissues. In cases of the most advanced disturbance of diabetic metabolisms, as occurs in diabetic coma, particularly if the patient has been emaciated, there is marked infiltration and increase in the fatty content of the liver and frequently there is an increase in the fat content of the blood. Unfortunately, there are not many figures available for comparison either in human beings or in animals. In human lungs, Root and Bloor[6] found phospholipid values of 0.94 and 0.89 and cholesterol values of 0.24 and 0.31 in non-diabetic lungs. Nevertheless, in 26 diabetic patients analyzed, some striking differences were found. Twelve cases had a phospholipid value exceeding 1.1 gm. per 100 cc. Only 3 of these cases were diabetics of short duration. One who died in coma had an area of healed tuberculosis in one apex. Another woman had healed tuberculosis and a fatty liver. Actually, 5 out of these 12 patients showed evidence of healed or healing tuberculosis at an apex. These fat-filled livers were present in 4 cases and in 5 there was lipoidosis of the spleen. Cholesterol values also showed some variation from normal. One interesting feature was a low phospholipid value in certain cases and this must be considered together with the low phosphorus content of diabetic cataracts, described from this hospital laboratory by Carey, Hunt, Waite and Beetham.[2] Since we know that the phosphorus metabolism is clearly linked with the carbohydrate metabolism, this may provide a clue which should be followed up.

Control of Diabetes by Insulin and Diet. The control of the diabetes as indicated by maintenance of normal weight, strength, avoidance of acidosis, excessive hyperglycemia and glycosuria is essential.

The use of insulin should never be omitted in any diabetic patient, particularly in early life or in middle life, if tuberculosis has ever been present or indeed, if known contact with an active, positive sputum case has been present. One-half of the patients treated at this hospital receive in the morning before breakfast a small dose of crystalline insulin combined with a dose of protamine zinc insulin. A practical advantage of protamine insulin in treating tuberculosis is its reduction of the frequency of injection. The fundamental advantage of protamine zinc insulin is the more regular control of the diabetes which is possible, especially when it is combined with a small dose of crystalline insulin. The action of crystalline insulin —as at present manufactured— is only a little more prolonged than that of regular insulin. However, it is a more pure product. Insulin reactions do occur in tuberculous patients with possibly greater ease than in non-tuberculous patients, particularly if the tuberculosis is far advanced, or if the patient is emaciated and, of course, if there has been an involvement by tuberculosis of the liver or adrenals with a destruction of their opposing function. The striking feature about patients with tuberculosis after a period of adjustment in the hospital, it is true, is that the amount of insulin required in cases with positive sputum has really been no greater than the amount required by patients of similar age without complications.

The diet of diabetic patients in general, but especially the diabetic patients with tuberculosis, should be superior in every respect to the average diet. I mean by this that every bit of modern knowledge of dietary objectives, not only with regard to the calories but with regard to the minerals and vitamins present in the diet should be utilized. The object of treatment should not be dictated solely by a regard for sugar-free urine and normal blood sugar, if that leads to a diet too poor in carbohydrate or too low in calories or to the use of unnecessarily large doses of insulin, which may provoke an overactivity of the counterregulatory and opposing influences in the organs. Glycogen impoverishment favors acidosis either of mild or threatening type, which in turn is most unfavorable to improving the resistance of the patient and, on the other hand, of itself it may prepare the way for serious hypoglycemia. Richardson's[5] experiments with depancreatized animals again indicate the value of liberal glycogen deposits in liver and skin in relation to infection. The use of a diet excessively high in fat, in patients who are emaciated or cachectic, may lead to such an increase of cholesterin in the blood as will favor vascular disease. Low values for cholesterol of the blood are usually accompanied by a special tendency to grave insulin reactions. We see no reason to believe that pulmonary hemorrhages are in any way due to insulin or produced by it. They are more likely due to overactivity of the opposing mechanisms with the outpouring of adrenalin, increased tone in the vessels and increase in blood pressure. In general, diets

of diabetic patients with tuberculosis should have from 150 to 225 gm. of carbohydrate and from 70 to 140 gm. of fat. A standard diet may be said to include approximately 150 gm. of carbohydrate, 80 gm. of protein, 100 gm. of fat, or a total of 2100 calories. A diet to increase weight might include 250 gm. of carbohydrate, 87 gm. of protein, 110 to 120 gm. of fat.

Case Abstract. As an example of our present dietary plan, I will cite the case of a young student, aged 18 years, at the onset of diabetes in September, 1926. His weight at that time was 110 pounds net and indeed he had never weighed any more. His father was of similar slender build. The diet prescribed at that time included 140 gm. of carbohydrate, 70 gm. of protein and 118 gm. of fat. In May, 1937, there was a small area of opacity observed in the fifth interspace posteriorly in the outer half of the chest about the size of a 25-cent piece. He spent some months at the state tuberculosis sanatorium and upon return this area had been replaced by a smaller area, somewhat more dense and the process seemed quiet. He had no fever and no cough. His weight remained unchanged. In the spring of 1939 Roentgen rays again showed a slight increase in the soft haziness at this area and again he spent several months in a sanatorium and was discharged arrested.

His present diet consists of carbohydrate 160 gm., protein 81 gm. and fat 116 gm.; total calories of 2016. His weight is 110 pounds and he is taking 7 units of crystalline insulin and 18 units of protamine insulin.

TABLE 1.—MINERAL AND VITAMIN VALUES IN DIET FOR CASE 6532, AGED 18 YEARS AT ONSET OF DIABETES IN 1927. PULMONARY TUBERCULOSIS DEVELOPED MAY, 1937. WEIGHT 110 POUNDS NET.

(Carbohydrate 160 gm., protein 80 gm., fat 116 gm., calories, 2016, crystalline insulin 7 units, protamine zinc insulin 18 units.)

Foods.	Amount, gm.	Ca, gm.	P, gm.	F, gm.	Vitamin A precursor carotene, I.U.	Vitamin B (thiamin), I.U.	Vitamin C (ascorbic acid), I.U.	Vitamin D (irradiated ergosterol), I.U.	Vitamin B^2 (riboflavin), microgms.	Nicotinic acid (pellagra preventive factor).
Milk	240	0.29	0.21	0.58	240	24	..	4.8	0.48	Fair
20% cream	120	0.12	0.21	0.48	1250	..	..	12.0		
Oatmeal	15	0.01	0.05	0.5	..	15	0	..	3.0	None
Orange	425	0.13	0.08	1.02	212	..	2000	..	33.0	Slight
Egg (1)	..	0.04	0.09	1.26	357	13	0	50	250.0	Fair
Bacon	15	..	0.03	0.02	0	26				
Butter	50	0.01	0.01	0.10	750	..	..	50	...	Slight
Bread (dark)	70	0.04	0.13	1.12	0	42	..	..	...	None
Meat	150	0.015	0.30	6.2	72	37	..	..	...	Good
Potato	180	0.02	0.11	1.53	54	36	270	..	17.0	None
5% vegetable	150	0.10	0.10	3.8	26790	45	1200	..	85.0	Fair
10% vegetable	180	0.10	0.09	1.04	5900	45	126	..	36.0	Slight
Cod-liver oil	5	..	..	..	10000	0	..	500.0	...	None
Totals	..	0.88	1.41	17.65	45625	283	3596	616.8	424.48	

NOTE: Whole-wheat or dark bread, spinach and lettuce among vegetables, are recommended and here calculated. Liver at least once a week.

If we run over the composition of this diet for essential mineral and vitamin values, we may begin with the calcium. Calcium content of the diet has special importance in diabetes since in diabetic patients with acidosis or diarrhea, both of which are common, there is a negative balance of calcium. It is by no means rare to have a thinning of the bones generally, so that in diabetic patients we have not only frequent fractures but sometimes spontaneous fractures, particularly of the spine in older patients. This patient's diet, then, containing milk and cream with a good deal of fruit juices, provides a total of 0.88 gm. of calcium, which is a normal figure. Phosphorus content is 1.4 gm., again normal; with iron there is a special relation again to diabetes in two ways. In the first place, hemochromatosis (or bronze diabetes) is by no means rare and this appears to be in some way a disorder of the iron metabolism. Secondly, anemia develops with greater ease in diabetic patients, particularly in the presence of complications and it is usually of the iron-deficiency type. This diet provides 17.6 mg. The vitamin A requirement, as shown on the cards which I have passed around, is more than 6000 I. U. The vitamin B_1 or thiamin is especially important in relation to diabetic neuritis and in this case the requirement of 200 units is well met. Vitamin C, vitamin D, vitamin B_2, riboflavin and nicotine acid are present in the amounts shown.

In order, however, to obtain a diet that is adequate one must remember certain simple requirements. In the first place, dark bread or whole cereals must be used. Vegetables rich in iron, including spinach and lettuce, are essential and liver should be included. Most of our diabetic patients should take some cod-liver oil at least during the winter months.

Summary. 1. In a review of the possible etiologic factors in 396 cases of pulmonary tuberculosis in diabetic patients, limitation in calories appeared to have less influence than lack of control of the diabetes.

2. Acidosis or coma preceded the development of tuberculosis in at least 20% and probably nearly 50% of the cases.

3. The use of insulin and diets adequate not only in the balance of carbohydrate, protein and fat, but in their content of vitamins and minerals is emphasized.

4. The tuberculosis death rate among diabetics per 1000 fell from 11 prior to the use of insulin to 4.1 during the first 6 years after the use of insulin.

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GASTROSCOPIC FINDINGS IN PATIENTS WITH DUODENAL ULCER.

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"Klinische Gastritisforschung ohne Gastroskopie ist nicht mehr möglich"—(Katsch: Handb. d. inn. Med., **1**, 455, 1938).

As is well known, there is a good deal of disagreement between the gastroscopic and the pathologic-anatomic conceptions of the pathogenesis of peptic ulcer.

Konjetzny[4] and those who agree with him claim that chronic ulcer is the end product of a primary chronic gastro-duodenitis that passes through the catarrhal stage and then the erosive stage, reaching its climax in the ulcerative stage with the formation of one or more chronic ulcers.

In contrast to this view, Schindler[5] and other gastroscopists look upon chronic peptic ulcer and gastritis as two different lesions without causal connection, and think that gastroscopy in most cases of chronic ulcer will not reveal any gastritis. Gastritic changes may appear only in cases where the ulcer gives rise to retention of the stomach contents; these changes are secondary and curable. In primary gastritis, it is true, ulcerations may appear; but they do not develop into chronic ulcers, as they are acute and transitory phenomena.

Pathologic and clinical observations by Faber[2] and Konjetzny have shown that symptomatically it often is impossible to differentiate between peptic ulcer and gastritis. Torben Andersen[1] even goes so far as to claim that the "pyloric syndrome" is not a symptom of ulcer, but a symptom of gastritis. In resected specimens from patients who were operated for gastric or duodenal ulcer, Konjetzny,[4] Faber, Christiansen and Paaby[3] and Vimtrup[6] found that several presented no peptic ulcer at all but an ulcerative inflammation on both sides of the pylorus.

While the pathologic-anatomic picture of the mucous membrane in chronic ulcer includes a multitude of slight and more severe changes, the gastroscopic findings, according to Schindler, are limited at the most to a few submucous hemorrhages or solitary small erosions along the lesser curvature; and this holds good, no matter whether the ulcer is located in the duodenum or in the stomach.

The divergence between these views is so wide as to call for further study and gastroscopic investigation; and an attempt at this will be made here. In the present paper, however, the author prefers to deal exclusively with duodenal ulcer, not with gastric ulcer, partly because the duodenal is the most frequent form of ulcer, but also because the conditions here are simpler and more perspicuous.

For that purpose the author has gone through his gastroscopic material, comprising over 500 patients with organic lesions of the digestive tract, and found altogether 70 cases of roentgenologically verified duodenal ulcer, that is, patients in whom the Roentgen ray examination* showed a constant and pronounced deformity of the duodenal cap, sometimes with a distinct notch. All cases in which the roentgenographic findings were doubtful and all cases of stenosis have been omitted. In none of these 70 cases was it practicable by relief examination to ascertain any changes in the stomach.

The patients were examined gastroscopically at a point of time when they had pronounced dyspeptic symptoms, and prior to the institution of treatment, so that an otherwise possible effect from the treatment upon the gastric mucosa can here be left out of consideration. Most of the patients were submitted to gastroscopic examination several times, a few of them up to ten times.

The present material comprises 13 women, aged from 23 to 53 years, and 57 male patients, aged from 13 to 64 years.

In 50% of the patients the lesion had persisted for more than 5 years, and most of them had gone through some form of medical treatment, or several cures in the course of time. About 20% of the patients were relatively recent cases, having had their symptoms for less than 1 year.

It will be reasonable to divide the material into groups based on the acidity of the gastric secretion as determined by means of the Ewald test meal, and first to consider the individual groups separately, noting whether definite gastroscopic features correspond to the different secretory groups of a clinical classification.

Such a classification of the material gives the following result:

Group A.	Normacidity (phenolphthalein 41–80°)	44 patients
Group B.	Hyperacidity (phenolphthalein 81–110°)	20 patients
Group C.	Hypacidity (phenolphthalein < 40°)	3 patients
Group D.	Anacidity (histamine-refractory achylia)	3 patients
	Total	70 patients

Group A. *Normacidity.* Of the 44 patients belonging to this group, 13 presented normal gastroscopic features, while it was possible in the remaining 31 patients to demonstrate more or less pronounced changes in the mucous membrane. In 19 patients these changes were those of a chronic superficial gastritis, and 6 patients showed features of chronic hypertrophic gastritis, while evidence of a beginning chronic atrophic gastritis ("patchy atrophy") was demonstrated in 1 patient. In 4 patients solitary erosions were demonstrated as the only gastroscopic abnormality, and 1 patient showed submucous hemorrhages along the lesser curvature in an

* In all these cases the Roentgen ray examination was carried out by Dr. de Fine Licht, Chief of the Department of Roentgenology, to whom I am indebted for painstaking collaboration through several years.

otherwise normal stomach. The occurrence of erosions in gastritic stomachs was seen but relatively seldom, only in 3 cases. Gastroscopic reëxamination after the discontinuance of treatment showed that the observed erosions all had healed without leaving any visible marks within 2 to 5 weeks, even in cases where no improvement of the gastritis could be demonstrated after the treatment. Finally, it is to be mentioned that 5 patients with gastritis showed also submucous hemorrhages, localized as usual.

The localization of the gastritic changes is evident from the following tabulation:

Localization.	Superficial gastritis.	Hypertrophic gastritis.	Total.
Entire stomach	5	3	8
Proximal half	14	3	17
Antrum alone	0	0	0

It will be noticed that in a majority of these cases (about two-thirds) the gastritis was localized exclusively to that part of the stomach which is proximal to the angulus, while in the other cases it extended over the entire stomach. An isolated affection of the antrum could not be demonstrated in any case. On the whole, it may be said that in most of the cases with gastroscopically demonstrable changes in the mucous membrane the affection consisted in the prognostically more benign superficial gastritis, while the prognostically more malignant hypertrophic gastritis was considerably less frequent; and the more severe degrees of the latter form of gastritis were not observed at all. So in this group, with normal gastric acidity, we find all three forms of gastritis represented. In other words, this group does not constitute any morphological entity.

The relation between the character of the symptoms and the gastroscopic findings is evident from the following survey:

Character of symptoms.	Gastroscopic findings.	
	Normal.	Pathological.
Pyloric syndrome	7	18
Pyloric syndrome + vomiting	1	4
Pyloric syndrome + hemorrhage	0	2
Uncharacteristic symptoms	5	7

From this it will be noticed that the typical ulcer symptoms—tardive pain, hunger pain, relief from intake of food, in some cases together with vomiting and hemorrhage—in duodenal ulcer are found far more frequently in those cases where the stomach is also affected than in cases presenting a normal stomach. On the other hand, there appears to be no particular difference in the frequency of the uncharacteristic symptoms, whether the stomach is gastroscopically normal or affected.

GROUP B.—*Hyperacidity.* Of the 20 patients belonging to this group, 5 presented a gastroscopically normal stomach, while patho-

logic conditions were demonstrated in 15, namely: chronic superficial gastritis in 13 cases, and chronic hypertrophic gastritis in only 1 case, while a solitary erosion in an otherwise normal stomach was seen in 1 case. In this group, submucous hemorrhages or atrophic changes were not observed at all.

The localization of the gastritis was as follows:

Localization.	Superficial gastritis.	Hypertrophic gastritis.	Total.
Entire stomach	7	0	7
Proximal half	6	1	7
Antrum alone	0	0	0

Even though the figures are rather small, they still show that there is no recognizable difference in the character, degree and localization of the gastritis in patients with duodenal ulcer, no matter whether the values for the acid secretion are normal or increased. This means that it is not justifiable from the finding of hyperacidity in duodenal ulcer to draw any conclusions as to whether the stomach is the site of a more severe form of gastritis than is encountered in patients with normal acidity. In particular, it is unwarranted to assume a preponderance of hypertrophic erosive elements corresponding to the findings in resected specimens. Finally, like Group A, this group corroborates the view that antral gastritis does not occur as an affection *per se* but merely as a part of a pangastritis. Hyperacidity in duodenal ulcer does not represent a gastroscopic entity.

The relation between the character of the symptoms and the gastroscopic findings in Group B is evident from the following survey:

	Gastroscopic findings.	
Character of symptoms.	Normal.	Pathological.
Pyloric syndrome	2	6
Pyloric syndrome + vomiting	0	2
Pyloric syndrome + hemorrhage	0	2
Uncharacteristic symptoms	3	5

This is in keeping with the findings in Group A, namely: that the typical ulcer symptoms are more frequent in duodenal ulcer patients with a gastroscopically affected stomach than in such patients with normal gastroscopic features, even though we have to be prepared among the former—duodenal ulcer patients with a gastroscopically affected stomach—to find several with quite uncharacteristic symptoms.

GROUP C.— *Hypacidity.* This group comprises only 3 patients, in whom the duration of illness was respectively 8, 6, and 3 years. Two of them had the pyloric syndrome without vomiting or hemorrhage; one had uncharacteristic dyspeptic symptoms. In the latter,

gastroscopy showed pronounced hypertrophic gastritis with erosive elements, localized to the upper two-thirds of the stomach, and most marked on the anterior wall, while the antrum appeared normal. One presented the features of a superficial pangastritis. In one the entire stomach looked normal.

GROUP D.—*Anacidity.* The 3 patients belonging to this group had had symptoms for respectively 1, 10, and 20 years. Two of them had a typical pyloric syndrome; the third had uncharacteristic dyspeptic symptoms. In the last 2 patients the stomach appeared normal, in the first there was a superficial pangastritis without erosions or hemorrhages. No atrophic area was seen in any of these cases.

The last two groups further illustrate the significance of gastroscopy to the clinical diagnosis of diseases of the stomach; and, like Groups A and B, they show that in patients with duodenal ulcer neither the clinical symptoms, nor the values for acidity, nor the Roentgen ray relief are serviceable criteria as to the state of the stomach.

Discussion. Considering the findings in these examinations as a whole, regardless of the secretory conditions, it turns out that in the 70 patients with duodenal ulcer it was practicable gastroscopically to demonstrate definite changes in the mucous membrane of the stomach in 49 cases (70%) while the gastroscopic findings were normal in 21 patients (30%).

The character and frequency of the various gastric findings are recorded in the following survey:

Gastritis, chronic superficial	34 patients
Gastritis, chronic hypertrophic	8 patients
Gastritis, atrophic	1 patient
Erosion in normal stomach	5 patients
Erosion in abnormal stomach	3 patients
Submucous hemorrhages in normal stomach	1 patient
Submucous hemorrhages in abnormal stomach	5 patients

So, in contrast to the view of Schindler, the gastroscopic findings show that the stomach in a majority of these cases was the site of pronounced pathologic changes. The most frequent finding was benign superficial gastritis, a form of gastritis that is curable. According to Schindler, in about 2% of the cases it subsequently turns into atrophic gastritis, a condition which in the present material was found in 1 patient. The next in frequency was the more serious and incurable hypertrophic gastritis. Solitary erosions occurred in several cases as the only pathologic finding as well as a gastritic phenomenon. The same applies to the submucous hemorrhages. In 17 patients the gastritic changes were distributed diffusely over the entire stomach, whereas in 25 patients they were localized exclusively to the proximal part of the stomach, corroborating the

view expressed by Schindler that antral gastritis does not exist as an affection *per se* but merely as part of a pangastritis.

The demonstrated frequency of gastritis in duodenal ulcer cannot be taken to confirm the findings of Konjetzny, however, as there is a considerable difference, qualitative as well as quantitative, between the changes here observed and those found in the resected specimens. Of course the objection may be raised, that gastroscopy can give information merely about the surface of the gastric mucosa, not about the deeper changes. But it must be kept in mind that the divergence does not concern microscopic findings, but, on the contrary, massive inflammatory changes in all the layers of the mucous membrane, which in resected specimens are visible also macroscopically on the mucosal surface where erosive, ulcerative and productive processes are found side by side. It has to be maintained that such severe changes cannot be overlooked by an experienced gastroscopist. In the present material, there is only one case where the gastroscopic picture of the mucosa corresponds to that which Konjetzny considers paradigmatic—namely, in a patient belonging to the hypochylic group who presented an erosive hypertrophic gastritis. If resection had been performed on this patient, however, the resected specimen would not have presented the picture Konjetzny emphasizes as typical, for here the gastritis was localized exclusively to the proximal part of the stomach.

Even though the findings here reported thus confirm only to a limited extent the features which Konjetzny and those who agree with him look upon as the general pathologic-anatomic finding, there can be no doubt that a gastroscopic picture corresponding exactly to this finding may be encountered in some cases. In such cases, then, the gastroscopic and the pathologic-anatomic findings may be quite in harmony morphologically. On the other hand, it will be difficult gastroscopically to find evidence in support of the conclusions Konjetzny and others have drawn concerning the etiologic and pathogenetic relationship between gastritis and chronic peptic ulcer, conclusions that once threatened to make resection of the stomach a standard therapeutic method.

To illustrate this point it will be appropriate to cite the case history of a patient not included in the material here concerned.

Case Report. An English scientist, 60 years old, for the last 3 years had been troubled by typical ulcer symptoms that were gradually getting worse during the last 6 months, and on which account he entered the hospital (Reg. No. Dep. B, 590/39). On admission, his general condition appeared to be fairly good. Hemoglobin: 107%. Blood urea: 32 mg. per 100 cc. Urine: No albumin or sugar; ++ chloride. Shortly after admission he commenced having copious watery vomiting, up to 500 cc. at a time. In connection herewith, azotemia appeared, with increase in blood urea to 72 mg. per 100 cc. and achloruria. As administration of vagospasmyl gave no improvement, treatment was instituted with daily gastric lavage and depositing of saline in the stomach. The azotemia yielded rapidly to this

treatment, but the pain persisted. Roentgen ray examination, one week after admission: Stomach filled with food remnants and fluid; pronounced gastrectasis with 24 hours' retention. Roentgenological diagnosis: Pyloric stenosis. Roentgen ray examination repeated one week later: Same findings as before.

Gastroscopy, 3 weeks after admission: Very marked gastritic changes throughout the stomach, but more pronounced superiorly on the posterior wall and along the greater curvature. Intense redness and succulence of the folds, which are thick, tortuous and studded with erosions. Between the folds, firmly adherent muco-pus. Angulus thick, dark red in color, glossy, eroded. The changes continue out in the canal. Through the pylorus, bile-colored duodenal juice squirts into the stomach. Gastroscopic diagnosis: Erosive pangastritis, severe degree.

After these findings further medical treatment seemed to offer only a poor outlook, and the advisability of an operation was considered. Under continued gastric lavage, however, the vomiting ceased, the pain subsided, and the patient gradually became able to tolerate a fever diet.

Roentgen ray examination after 3 weeks' continued gastric lavage showed: Relief more conspicuous. After filling, the stomach is large and atonic, yet far smaller than before. The emptying proceeds more lively, so that the duodenum fills better. The duodenal cap is constantly deformed, with eccentric location of the pyloric inlet and considerable dilatation of the lateral recess, possibly a notch, so that there can be no doubt about the presence of a duodenal ulcer. Four hours after intake of the contrast meal the stomach has emptied completely.

After these roentgenographic findings and the marked improvement in the condition of the patient, there was no longer any reason to consider surgical treatment.

Gastroscopy, 16 days after the first examination: The pyloric part, the antrum and the lower half of the stomach are perfectly normal as to color, juiciness and structure. No erosion is seen, nor mucus between the folds. Superiorly, below the cardiac orifice there are still some remnants of the gastritis as redness, succulence and increased vulnerability. Inferiorly, toward the greater curvature, there is a single pea-sized erosion on the anterior wall.

Next day the patient was discharged from the hospital, free from symptoms.

This case is instructive, and it possibly can give an explanation of the divergence between Konjetzny and Schindler. There can hardly be any doubt that if resection had been performed on this patient, as was at one time considered when his illness was at its worst, the resected specimen would have presented macroscopically as well as microscopically the very picture on which Konjetzny and his followers base their theories. There would have been a duodenal ulcer together with a violent, erosive, antral gastritis. The course of the disease showed, however, that these pronounced changes were of an acute character, healing within a few weeks, when the pyloric spasm subsided and the retention disappeared.

To those who have had the opportunity gastroscopically to follow such a case—which is by no means unique—the question suggests itself, whether the changes found in the resected specimens really are not to be looked upon as being of a similar nature as the ones observed in this patient. The whole course of the disease as re-

corded here, with an almost miraculous improvement of the clinical symptoms running parallel with a rapid healing of very severe changes in the stomach, while the roentgenographic changes in the duodenum remained constant, may hardly be interpreted otherwise than indicating that the duodenal ulcer in this patient is the primary lesion while the gastritis is secondary. At any rate, it will be difficult from the recorded observations to find anything in support of the contrary view.

Summary and Conclusions. 1. It may be taken as the general rule that patients with a non-stenotic duodenal ulcer are liable to pathologic changes in the gastric mucosa, even though no abnormality may be demonstrated by roentgenography or Ewald test meal.

2. Deviations from normal acidity furnish no basis for conclusions about the character of these changes or their location in the stomach.

3. To settle the question about the state of the stomach gastroscopy is the method of examination.

4. The gastric changes include all three forms of gastritis, the preponderant being the relatively more benign chronic superficial gastritis, which in some cases possibly may go on to atrophy. Chronic hypertrophic gastritis is more serious but less frequent. Solitary erosions and hemorrhages may make their appearance as elements of a gastritis or as the only gastroscopic abnormalities. The same applies to the punctate submucous hemorrhages.

5. The gastritis may be total or partial; in the latter case, it is localized to the fundus of the stomach. If the antrum is involved, it is always as part of a pangastritis, whereas an isolated antral gastritis is not seen gastroscopically.

6. The erosions are acute manifestations that may heal in a few days, no matter whether or not the gastritis improves at the same time. Transition to a chronic gastric ulcer has not been observed.

7. The typical ulcer symptoms seem preferably to make their appearance in cases where the stomach is also affected.

8. Acute gastric retention may be associated with severe erosive changes in the stomach corresponding to the findings in resected specimens. These changes are inconstant and may disappear rapidly when the retention subsides. Probably this condition does not involve a primary gastritis, as has been claimed by Konjetzny, but more likely secondary peptic injury, as asserted by Schindler.

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INVERTED DUODENUM.

Its Clinical Significance With Report of 14 Cases.

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In recent years there has been considerable interest shown in diseases and anomalies of the duodenum. In this communication an anomalous condition in the form of an inverted duodenum is presented with a report of 14 cases. Anomalies of the first portion of the duodenum are very rare, since it arises from the foregut. Most anomalies of the intestine arise from errors of rotation of the midgut. Inverted duodenum is a congenital anomaly due to a developmental error involving the caudad segments of the duodenum. The condition is not common, but occurs more often than a survey of the literature would indicate. Bryce[2] and others consider it a rare anomaly.

The true incidence of this anomaly has not been determined as far as one can ascertain from the literature. The roentgenologic incidence of inverted duodenum is extremely low. In approximately 20,000 gastro-intestinal Roentgen studies 14 instances (0.07%) have been observed. Anderson[1] noted the condition to occur once in the examination of 100 consecutive subjects in the dissecting room. The incidence of 1% in his study seems to be rather high. The total number of reported cases has not been tabulated. Sandera[4] reported 10 cases, 2 of which were confirmed by operation. Weinbren and McGregor[5] reported 11 cases, and Hurthle[3] 5 cases.

This anomaly has been described as a form of mobile duodenum to which Sandera gave the term of "duodenal dystrophy." Duodenum inversum is described as a transitional type of mobile duodenum, but he believes that it is not a true form of mobile duodenum. The fact that the various groups of mobile duodenum are not sharply defined probably accounts for its description under various headings. There has been a tendency in recent years to segregate the different forms of duodenal abnormalities into definite entities. Sandera deserves credit for pointing out and giving a full description of the varieties of mobile duodenal abnormalities.

The association of other congenital anomalies coexisting with inverted duodenum should be emphasized. However, in our series of 14 cases, which do not include those with non-rotation of the intestines, there were no other gastro-intestinal anomalies that could be recognized by means of the Roentgen examination. In cases of

inverted duodenum, evidences of defective mesenteric attachment have been observed. There may be changes in position and shape of the head of the pancreas, and other pancreatic anomalies.

The condition may be found at any age. In our 14 cases the ages ranged from 26 to 67 years (average, 47 years); in Weinbren and McGregor's 11 cases, from 26 to 70 years. The average age in Sandera's 10 cases fell in the third decade. The condition predominates in the male sex. In our series, there were 11 males and 3 females. In Weinbren and McGregor's 11 cases, 7 were males and 4 females.

Clinically, this anomaly presents no characteristic symptoms or signs which might aid in the diagnosis. It is probable that this condition often exists without giving rise to any symptoms whatever, and, on the other hand, many of the symptoms may arise from an associated lesion or complication. Epigastric pain or discomfort, nausea, belching and gaseous distention are the most prominent symptoms encountered in this condition. However, jaundice and diarrhea are not uncommon. Table 1 presents the pertinent symptoms and associated conditions observed in our 14 cases. When stasis occurs as a result of this anomaly a certain train of symptoms may appear depending upon the degree of stasis. Among these may be mentioned loss of appetite, nausea, epigastric discomfort, vomiting and headaches, often of the migraine type. In some, so-called bilious attacks may occur at varying intervals, usually preceded by periods of constipation. When these attacks are frequent, loss of weight and strength supervene and in certain individuals neurasthenic symptoms become a prominent part of the picture.

In our 14 cases the symptoms varied, and seemed to be due to the associated or complicated conditions. Symptoms of peptic ulceration were most common, but only 5 of our cases presented roentgenologic signs of peptic ulceration. According to Sandera, symptoms are due to the hindering of the passage of the duodenal contents. He found that nearly all of his patients complained of abdominal pain, discomfort after eating and spells of fulness and nausea. It has been pointed out that this condition may predispose to pancreatitis and cholecystitis as a result of secondary involvement through the ducts. Ordinarily, however, these complications do not occur unless there is an anomalous development, change of position or twist of the bile duct in consequence of the abnormal curve of the duodenum or they may be due to stasis in the duodenum causing a back-flow through the ducts into the pancreas or gall bladder.

The following brief abstract of one of our cases illustrates some of the clinical aspects of an inverted duodenum case associated with a mild cholecystitis.

Mrs. R. W. B., aged 55, complained of belching, nausea, regurgitation of bile, loss of appetite, vague abdominal pains and loss of weight over a period of 5 years. Recently she had noticed evidence of jaundice. Physical

TABLE 1.—SUMMARY OF CLINICAL DATA IN 14 CASES OF INVERTED DUODENUM.

Cases.		Sex.	Age.	Pain.	Appetite.	Constipation.	Vomiting.	Gas belching.	Nausea.	Loss of weight.	Jaundice.	Headache.	Test meal.		Associated conditions.
													Free HCl.	Total.	
1	H. L.	M	57	+	Poor	+	+			+			0	18	Carcinoma of stomach.
2	F. S.	F	42	+	Poor	+		+				+	57	78	Gall stones, duodenal diverticulum and stasis.
3	S. J. S.	M	61	+		+				+					Mediastinal neoplasm.
4	F. L.	M	54		No	gastro	-intest	inal sy	mpto	ms.			56	82	Pulmonary tuberculosis.
5	F. W. V.	F	45	+	Poor								39	58	
6	F. S. J.	M	28	+	Poor	+		+							
7	J. B.	M	67	+									36	54	Gastric ulcer; pyloric obstruction.
8	H. K. D.	M	40	+	Poor								38	56	Peptic ulcer.
9	J. T.	M	54	+		+									
10	A. M.	M	26	+	Good								50	58	
11	C. H. B.	M	38	+			+			+					Gastric ulcer.
12	R. M.	M	43	+				+							Duodenal ulcer.
13	M. P.	M	44	+	Good										Duodenal ulcer.
14	R. W. B.	F	55	+	Poor			+	+	+	+		10	32	Low-grade cholecystitis.

examination was essentially negative. Urine was normal. Wassermann was negative. An Ewald test meal yielded a total acidity of 32, and free hydrochloric acid of 10. A gastro-intestinal Roentgen study revealed a normal stomach and duodenal bulb; there was an absence of the duodenal curve with a Type 2 inverted duodenum. Cholecystography revealed a gall bladder of poor density; there were no stones. Following a fat meal there was delayed emptying. A diagnosis of inverted duodenum, associated with a low-grade cholecystitis was made.

The Roentgen examination offers the only means by which a correct diagnosis can be made. A careful study of the entire course of the duodenum will clearly depict this condition. It is radiologically characterized by the anomalous position and course of the duodenum, with either shortening or lengthening of the duodenum. Several varieties of inverted duodenum may be demonstrated roentgenologically, depending upon the segment at which the developmental error occurred. The position of the duodenal bulb is never involved in this condition.

For the purpose of description we have divided this anomaly into four types. In the first a complete inversion of the entire duodenum (excepting the bulb) is observed. The entire duodenal curve is absent and its course and direction are completely changed. Instead of the descending duodenum being directed downward in the right mesial aspect, there is an elimination of the angle formed by the bulb and the second portion of the duodenum. The direction of the duodenum extends upward toward the left and backward. The third and fourth portions of the duodenum are not demarcated, cross the mid-line transversely to the left toward the duodenojejunal juncture. The composite picture reveals an absence of the duodenum in its normal position with complete absence of the normal duodenal C-shaped curve. In this form, the duodenum is on a higher level and is shorter than normal (Fig. 1).

In the second type, the inversion takes place in the descending arm or second portion of the duodenum at the angle with the third or transverse segment. The normal duodenal curve is again absent. The second portion appears to extend down in its normal position, or it may be pulled over to the right and upward. Instead of the

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Legends for Figs. 1 to 3.

Fig. 1.—(Left) normal duodenal curve. (Right) Type 1 variety of inverted duodenum. Note the position of the duodenum, with complete absence of the curve. The duodenum is shortened and shows an absence of the normal demarcation of its different segments.

Fig. 2.—Two varieties of Type 2 inverted duodenum. Note the change in the direction of the duodenum which begins at the angle between the descending and transverse segments. Also note the upward direction of the ascending duodenum which occurs to the right of the descending arm.

(Left) duodenum crossing the midline behind the duodenal bulb.

(Right) duodenum crossing the midline behind the duodenal bulb.

Fig. 3.—(Left) Type 3 inverted duodenum, presenting a redundancy of the superior duodenum, with lengthening of the duodenum.

(Right) Type 4 inverted duodenum illustrates a complete inversion of the duodenum in a case of congenital non-rotation of the intestine.

1

2

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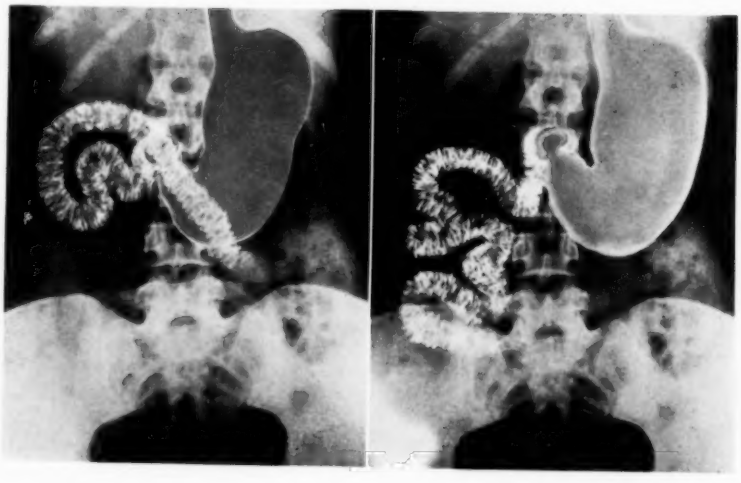

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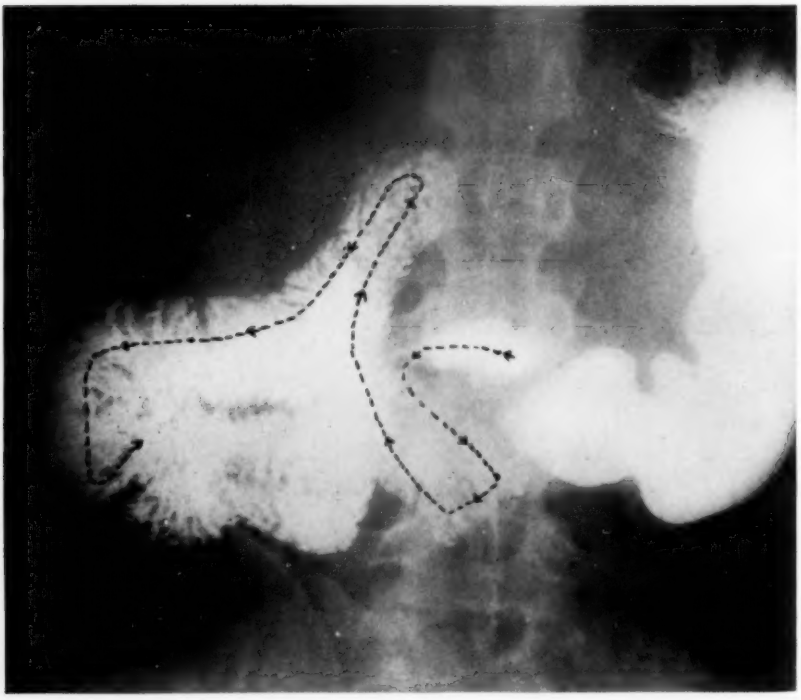

5

third portion crossing transversely toward the left, this segment makes a sharp upward and outward turn towards the right side, and then ascends to the right of the descending arm, crossing behind or over the duodenal bulb. The duodenum is apparently of normal length (Figs. 2 and 4).

The third type reveals a lengthening of the duodenum, an absence of the normal duodenal curve and marked redundancy of the superior duodenum. The course of the duodenum is similar to that of the second variety, except that in this form there is a lengthening of the duodenum with a sagging loop. The position of the duodenum is displaced to the right. The duodeno-jejunal juncture may also be displaced mesially (Fig. 3).

In the fourth type, there is not only an inversion of the duodenum but in addition a congenital non-rotation of the intestine, with the entire duodenum situated on the right side of the abdomen. In this form there is an absence of the duodeno-jejunal angle; the duodenum joins the jejunum on the right side of the abdomen (Figs. 3 and 5).

It must be pointed out that the duodeno-jejunal angle may be abnormally situated. The position of the stomach may be directed further to the left than normal. The position of the stomach in our 14 cases was normal. Weinbren and McGregor noted that the stomach may be further to the left of the spinal column than usual. In the true form of inverted duodenum the position of the duodenal bulb is relatively normal and does not appear to be involved in the anomalous position of the remaining duodenum. Our studies did not reveal any change in the position of the duodenal bulb. Occasionally it may be directed transversely.

Changes in the motility of the duodenum are often observed. In the first type, it usually empties rapidly, while in Types 2 and 3 it may be retarded, especially in the latter variety, where varying degrees of stasis with dilatation of the lumen may be observed. In the cases presenting duodenal stasis there may be secondary involvement of the pancreatic, biliary and hepatic structures. In the redundant variety, there is nearly always a stasis with disturbance of motility of the superior duodenum. In the fourth type, with non-rotation of the intestine, duodenal motility is generally accelerated.

The stomach ordinarily empties normally in most instances. In our 14 cases there was no delay in emptying. Sandera and Hurthle likewise found no delay in the emptying time of the stomach. However, Weinbren and McGregor observed a slowing of the emptying rate in 3 of his 11 cases.

LEGENDS FOR FIGS. 4 AND 5.

FIG. 4.—A typical case of inverted duodenum, with complete absence of the duodenal curve. Note direction of the duodenum at arrows.

FIG. 5.—Inversion of the duodenum in a case of partial non-rotation of the intestine. Note the absence of the normal duodenal curve and change of position of the duodeno-jejunal flexure from the left side to the right.

In the Roentgen examination of the duodenum care must be taken to obtain a full and clear view of the entire duodenal curve. Fluoroscopic examination is most important in portraying this anomaly. Prone, supine, lateral and oblique views are often required completely to visualize the whole course of the duodenum. Even with the above positions the distal portion of the duodenum may be overshadowed by the stomach so that the complete curve and course are obscured. A duodenogram, in which the opaque meal is placed directly into the duodenum through a tube, is an ideal procedure to bring out the whole course of the duodenum, of which it gives a clear unobscured view.

In the treatment of this condition conservative medical management is usually sufficient to bring about symptomatic relief, especially since in the majority of these cases periods of well-being are quite characteristic. In those cases in which the associated lesion is responsible for the clinical manifestations, treatment necessarily is directed towards overcoming the underlying disease. To accomplish this, it might occasionally be advisable to conduct a rest cure in bed, preferably in a hospital, for from 4 to 6 weeks, during which time general upbuilding measures might be instituted in addition to the therapy of the underlying condition. When duodenal stasis is marked, transduodenal lavage with magnesium sulphate or Ringer's solution is usually very beneficial. The diet should be of the bland type and of a high caloric and vitamin content. When adequate medical management fails to bring about relief, surgical intervention may become necessary. The type of operation performed will depend not only upon the patient's condition but also on the lesions discovered after a thorough exploration.

Summary. Anomalies of the duodenum are far more common than is indicated by a survey of the literature. Of these, the inverted duodenum is of considerable interest. Fourteen cases are here recorded. Since the roentgenologic incidence of this condition occurs in only 0.07% of cases, it was considered of general interest to report this series. A detailed radiologic description of the anomaly is given, together with an anatomic classification. Clinically, there is no characteristic symptomatology, the picture being often that of a complication or an associated lesion. Many instances undoubtedly occur without presenting any symptoms whatever. The diagnosis must be based on a thorough Roentgen-ray investigation. These cases deserve careful study not only from an anatomic standpoint but also from the clinical aspect, since their early recognition and effective treatment may prevent the occurrence of secondary conditions such as cholecystitis and pancreatitis.

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THE USE OF SULFAPYRIDINE IN STREPTOCOCCUS VIRIDANS MENINGITIS.

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Sulfapyridine has been used successfully in the treatment of pneumococcus pneumonia and pneumococcic meningitis,[1] and according to recent reports it offers hope in sub-acute bacterial endocarditis.[2] To date, we know of no reports on its use in meningitis due to streptococcus viridans.

Since January, 1937, we have treated 6 cases of streptococcus viridans meningitis. Two were treated with sulfapyridine and recovered; 1 with sulfanilamide, sulfapyridine, Uleran,* and deep Roentgen ray therapy, and recovered; 3 were treated with sulfanilamide and failed to improve.

Case Abstracts. Case 1.—W. J. L., a 54-year-old negro, admitted to the Genito-urinary Service May 16, 1939, had complained for about 1 year of recurrent attacks of urinary retention relieved by passing of blood clots or catheterization, followed by hematuria.

Physical examination was negative. Cystoscopic examination revealed blood oozing from the right ureter. A retrograde pyelogram revealed numerous small stones in the left middle calyx. The upper calices on the right had a peculiar sharp configuration, and the base of the upper major calyx was quite wide, which was interpreted as possible scarring due to a calculus. Guinea pig inoculation and smears of urine were negative for acid-fast bacilli.

On the sixth day after admission he had a chill, an hour and a half later, a convulsion, and his temperature rose to 104°. Blood non-protein nitrogen taken at this time was 36 mg. per 100 cc. Within 24 hours opisthotonos was present, neck rigid, Brudzinski and Kernig's signs positive. Spinal puncture revealed turbid fluid, positive globulin, and 230 cells, predominantly polymorphonuclears. He was transferred to the Communicable Disease Service, where another spinal puncture was done and 8500 cells were found; direct smear of spinal fluid showed no organisms. He was placed on sulfanilamide and given 90 grains before the spinal fluid culture report of streptococcus viridans was received. The treatment was changed to 2 gm. of sulfapyridine every 4 hours, and the same dosage was maintained for 8 days. Two days after starting the drug the temperature returned to normal. On the third day, the spinal fluid cell count dropped to 450 and cultures were negative.

* Uleran (dimethyl disulfanilamide) was furnished by Winthrop Chemical Company, Inc.

The patient made an uneventful recovery, and after having been with us for 20 days was returned to the Genito-urinary Service.

SPINAL FLUID EXAMINATIONS.

Date, 1939.	Cells.	Smear.	Culture.
5/23	8500	Negative	Strep. viridans
5/24	..	"	" "
5/25	..	"	" "
5/26	Bloody	"	" "
5/27	450	"	Negative
5/28	200	"	"
5/29	100	"	"
5/30	50	"	"
6/1	40	"	"
6/6	35	"	"

CASE 2.—J. D. W., a 22-month-old white boy, admitted to the Communicable Disease Service August 4, 1939, had been ill for 1 month with alternating periods of diarrhea and constipation. One week before admission the diarrhea became marked and slight fever developed. Two days later, fever became high (not taken), the child vomited frequently, and refused to eat. This situation persisted to the time of admission. Physical examination revealed a poorly nourished, dehydrated male child of 22 months, having frequent generalized convulsions. Rectal temperature 104.2°, pulse 96, respiration 48. The eyes rotated aimlessly; both ear drums were red; neck was rigid; Brudzinski and Kernig's signs positive.

Spinal fluid, under a pressure of 400 mm. of water, contained 1900 cells, mostly polymorphonuclears. Smear revealed Gram-positive diplococci and culture contained streptococcus viridans. Bilateral myringotomy was done on admission and for 2 days a slight serous drainage followed. Sulfapyridine was given 1 gm. every 4 hours. Spinal fluid on the day after admission contained Gram-positive cocci on direct smear, but the culture was negative. The temperature returned to normal on the 5th day. The patient was discharged on the 20th day.

SPINAL FLUID EXAMINATIONS.

Date, 1939.	Cells.	Smear.	Culture.
8/4	1900	Gram-pos. cocci	Strep. viridans
8/5	1750	Gram-pos. cocci	Negative
8/6	700	No organisms	"
8/7	500	" "	"
8/8	Bloody	" "	"
8/9	200	" "	"
8/10	200	" "	"
8/11	Bloody	" "	"
8/14	100	" "	"
8/17	Bloody	" "	"
8/23	3	" "	"

CASE 3.—E. U. S., an 8-year-old white boy admitted to Communicable Disease Service September 20, 1939, had complained of headache, fever up to 103°, nausea and vomiting, pains in the legs and stiff neck of 3 days' duration. He had had pneumonia 5 months previously, and had not been well since. On admission temperature was 101.8°, pulse 120, respiration 24. His neck and back were stiff, Brudzinski and Kernig's signs positive. It was thought that there was weakness of both upper and lower extremities, although reflexes were all physiologic.

Spinal puncture revealed pressure of 150; 79 cells, 66% polymorphonuclears; no organisms on direct smear, and no growth on culture. A diag-

nosis of poliomyelitis was made, and 100 cc. of convalescent poliomyelitis serum were given. On the third day difficulty in swallowing developed, and Retan's[3] method of treatment was started. The next day spinal fluid cell count jumped to 1800 and the succeeding day to 12,600 with 90% neutrophils. A blood culture taken at this time produced streptococcus viridans a few days later.

Diagnosis was changed to meningitis and sulfanilamide was started. After 24 hours this was changed to sulfapyridine. Two days later spinal fluid cultures were reported positive for streptococcus viridans. Roentgen ray of sinuses and mastoids revealed no lesions and on aspiration of the sphenoid sinus no pus was found. After 5 days of sulfapyridine, no improvement was noted so sulfanilamide was started again. Cultures remaining positive, sulfapyridine again replaced sulfanilamide after 3 days. Spinal fluid cultures became negative 2 days later, but the spinal fluid cell count and general condition did not improve. Because of this, Uleran was started and deep Roentgen ray therapy was given to the base of skull. Clinical improvement was marked within 24 hours. The spinal fluid cell count dropped to 47 within 72 hours, and the temperature to normal on the fifth day. Thereafter, all medication was stopped and recovery was uneventful.

SPINAL FLUID EXAMINATIONS.

Date, 1939.	Cells.	Smear.	Culture.
9/20	79	Negative	Negative
9/23	108	"	"
9/25	1800	"	"
9/26	12600	"	Strep. viridans
9/27	10000	"	" "
9/28			
9/29	980	Negative	Strep. viridans
9/30	195	"	" "
10/1	212	"	" "
10/2	1500	"	" "
10/3	990	"	" "
10/4	895	"	" "
10/5	1260	"	" "
10/6	620	"	" "
10/7	410	"	" "
10/8	500	"	No growth
10/10	225	"	Strep. viridans
10/12	840	"	No growth
10/14	433	"	" "
10/16	47	"	" "
10/20	10	"	" "
10/22	18	"	" "
10/24	16	"	" "
10/26	10	"	" "
10/28	10	"	" "
11/5	7	"	" "

Conclusions. While definite conclusions cannot be drawn from merely 3 cases, it would seem that sulfapyridine was responsible for the recovery of 2 of these patients and had an inhibiting effect on the organisms in the third case.

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THE SABIN AGGLUTINATION TEST AS A CONTROL OF THE SULFAPYRIDINE TREATMENT OF PNEUMONIA.

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Recovery from pneumonia is believed to be dependent upon destruction of the pneumococci by phagocytes. For the phagocytes to accomplish this, however, there must be adequate type-specific antipneumococcic antibody.

In 1902 Neufeld[3] observed in patients recovering spontaneously from pneumonia that antibodies for the homologous pneumococcus first appeared in the blood about the time of the crisis. This was usually early in the second week of the disease in uncomplicated pneumonia. In the treatment of pneumonia with sulfapyridine, some of the first investigators noted that the marked improvement seen in the first 24 hours was deceiving. For when the drug was stopped soon after the early defervescence of fever, relapse occurred frequently, sometimes with spread to new lobes or other complications. Like many others, we had noted that when sulfapyridine was continued until the eighth or ninth day of the disease there were few relapses. As mentioned above, this corresponds with the time when antibody first appears in the blood of patients recovering from pneumonia spontaneously. By a simple slide agglutination method we determined when antibodies first appear in the blood of patients with pneumonia treated with sulfapyridine, and believe that this may indicate when it is safe to discontinue treatment. In 1929 a microscopic slide method was described by Sabin[4] for the detection of specific pneumococcic agglutinin in the blood. Since then, this method has been used as a guide to the adequacy of serum therapy by several physicians having a large experience with pneumonia. There is some difference of opinion, however, concerning the value of the agglutinin test as a guide to serum dosage.[1,2] Some feel that it is too delicate a test; that is, a patient with a strongly positive agglutinin test still may need more serum. It is

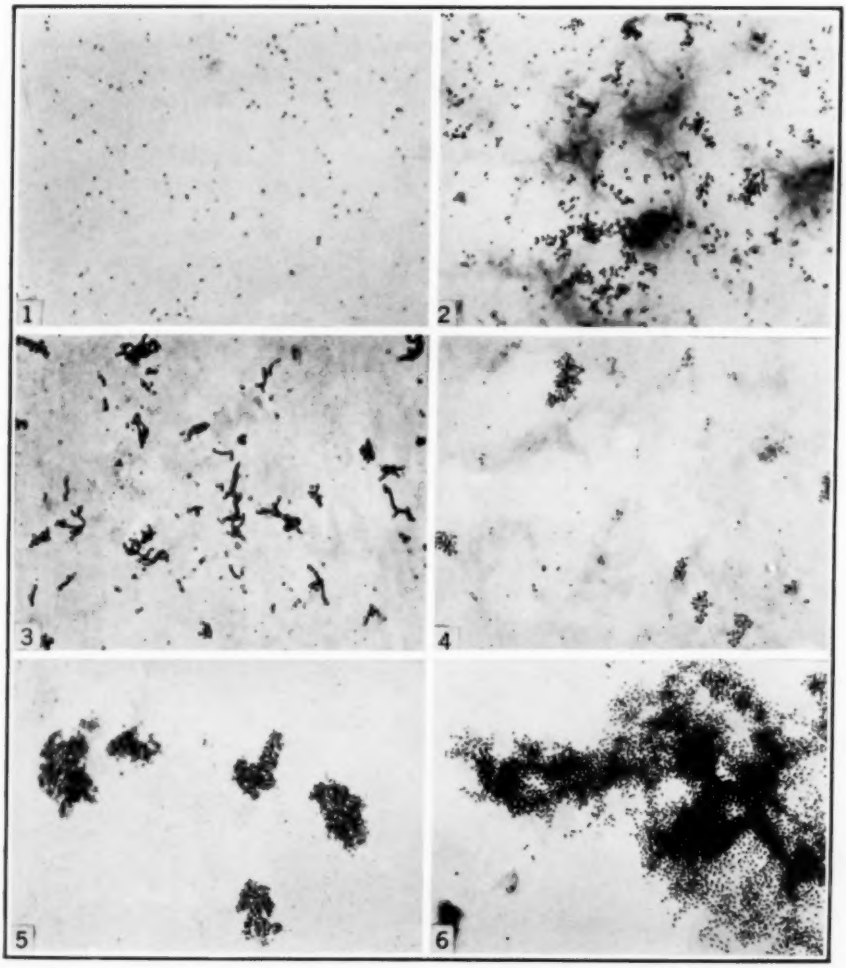

FIG. 1, Negative agglutination. FIG. 2, 1 + agglutination. FIG. 3, 1-2 + agglutination. FIG. 4, 2 + agglutination. FIG. 5, 3 + agglutination. FIG. 6, 4 + agglutination. (Fig. 3 illustrates appearance of test when antigen is "rough," *i. e.*, consists of pneumococci in chains.) Reactions of 2-3 +, or greater, are significant of active specific immunity.

not the purpose of this paper to enter this dispute but to indicate that when specific agglutinin appears in the blood spontaneously in patients who have not received serum, it is a reliable indication of the development of active immunity and as such can be used as a control for the continued administration or withdrawal of sulfapyridine. The final decision depends on the presence or absence of complications.

The present study represents a total of 275 agglutinin tests made at frequent intervals during the course of pneumonia in 50 adult patients treated with sulfapyridine. The slide agglutination technique as described by Sabin was the method used. Blood was collected in a small glass capillary from a puncture of the ear or finger, as in performing a coagulation time. The contents were expelled on a glass slide from the capillary by means of a small rubber bulb (such as accompanies a smallpox vaccination outfit). The clot is easily lifted off with a hot wire, leaving the serum almost

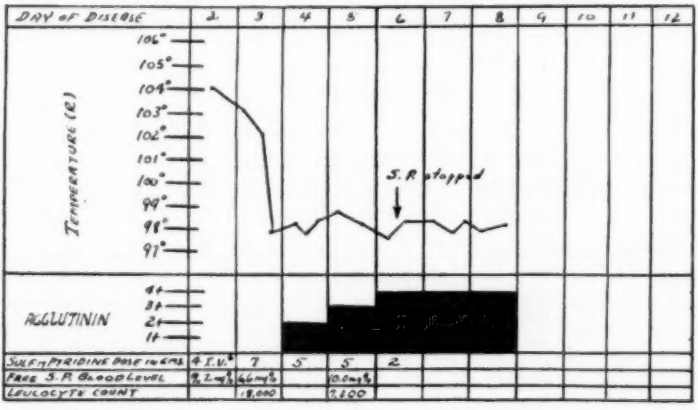

CHART 1.—J. B. ♂ 35 Type I pneumococcic R.L.L.-R.M.L. Pneumonia. Sulfapyridine stopped when agglutinin = 4+

* Intravenous sodium sulfapyridine.

clear. The test was performed by mixing on a slide a loopful of formalized pneumococci† of the homologous type with a drop of the patient's serum and allowing it to dry in air. The film was fixed with heat and laked by covering it with modified Ruge's solution (4% formaldehyde and 1% acetic acid). It was then rinsed with water, stained with crystal violet or carbol fuchsin, and examined with the oil immersion lens. The degree of agglutination was recorded in accordance with the following scale: 0, 1+, 2+, 3+, 4+; 0 representing no agglutination and 4+ complete agglutination (Charts 1–6).

Charts 1 to 6 illustrate representative cases.

† Suspensions of Types 1 to 30 pneumococcus were supplied by the Lederle Laboratories, Inc.

Charts 1 and 2 are of patients with uncomplicated pneumonia without bacteremia to whom sulfapyridine was administered until the agglutinin test became markedly positive. Uneventful recovery followed.

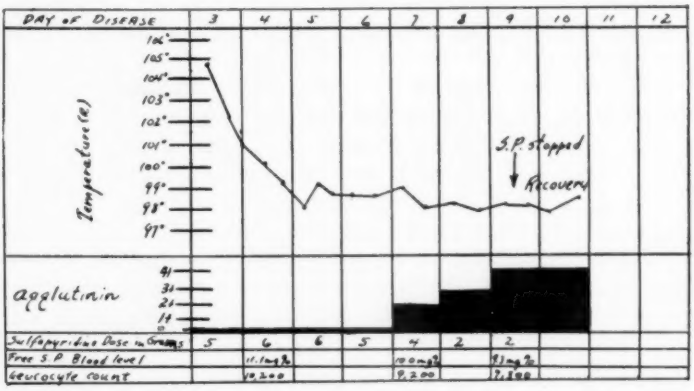

CHART 2.—W. C. ♂ 35 Type I pneumococcic R.L.L. pneumonia. Sulfapyridine stopped when marked agglutination occurred.

Chart 3 is that of an uncomplicated pneumonia with bacteremia which persisted for one day after the temperature had dropped to normal. Sulfapyridine was continued until the 11th day of the disease when the agglutinin had become 2+. (At that time also

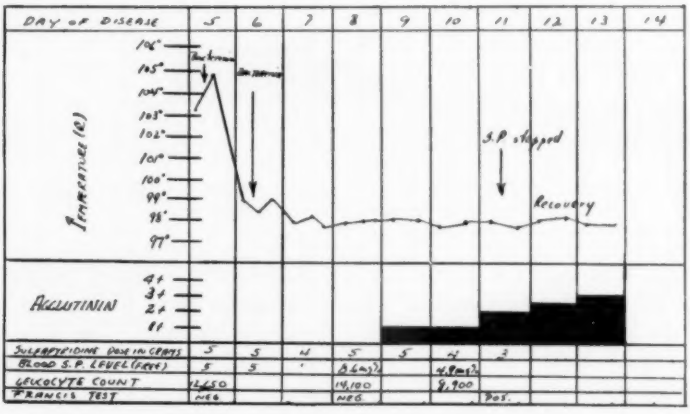

CHART 3.—B. L. ♂ 41 Type VII pneumococcic R.U.L. pneumonia with persistent bacteremia. Agglutinins appear late—S. P. continued until agglutinins become strongly positive.

the Francis test with homologous type polysaccharide solution became positive. Both the agglutinin and Francis tests were negative prior to that date. Studies now in progress attempting to

correlate the two tests as indices of active immunity in sulfapyridine-treated pneumonia will be described in a subsequent report.)

Chart 4 is of a patient who, in spite of a high free sulfapyridine level in the blood, had delayed resolution and ran an irregular fever.

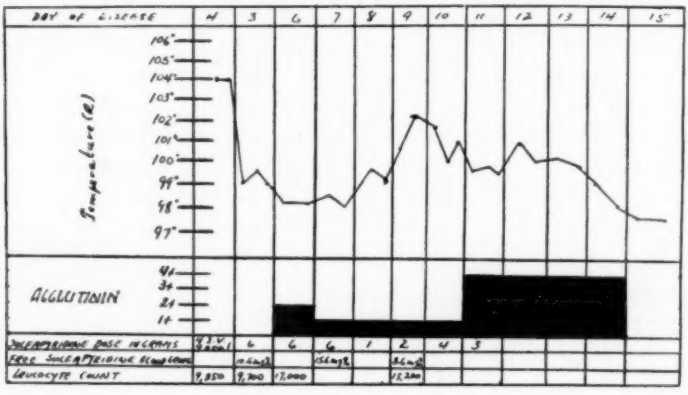

CHART 4.—♂ 27 Type II pneumococcic R.U.L. pneumonia. Irregular fever and delayed resolution, in spite of good sulfapyridine blood level. Sulfapyridine continued until agglutinins became 4+.

Sulfapyridine was not discontinued, therefore, until the 11th day of the disease, at which time the agglutinin test became markedly positive. Thenceforth, recovery was uneventful.

Chart 5 is of a patient with Type II pneumococcic pneumonia,

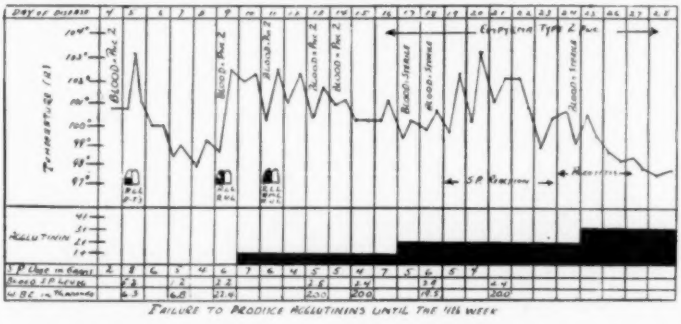

CHART 5.—J. N. ♂ 41 Type II pneumococcic pneumonia with persistent bacteremia-spread and empyema. Failure to produce agglutinins until the 4th week. Low blood sulfapyridine level, initial leukopenia, and absence of agglutinin allowed spread of infection.

initial bacteremia and low white blood count. In spite of large oral doses of sulfapyridine, he failed to maintain an adequate blood sulfapyridine level. On the 9th day of his disease the pneumonia spread from the right lower lobe to the right upper lobe and the

blood culture was again positive for Type II pneumococci. For the next 6 days the blood contained Type II pneumococci and during this time the right middle lobe became involved, and finally signs of empyema developed. At no time were agglutinins for Type II pneumococci present in more than 1+ concentration. On the 18th day of the disease they became more definitely positive (2+). On the next day signs of toxic reaction to sulfapyridine first appeared and on the 20th day the drug was withdrawn (somewhat reluctantly for fear of more spread or blood stream invasion). After withdrawal of sulfapyridine, however, the blood remained sterile. On the 27th day, the temperature had returned to normal in spite of recurrent delirium tremens and a mild parotitis. At this time the agglutinins for Type II pneumococci were strongly positive

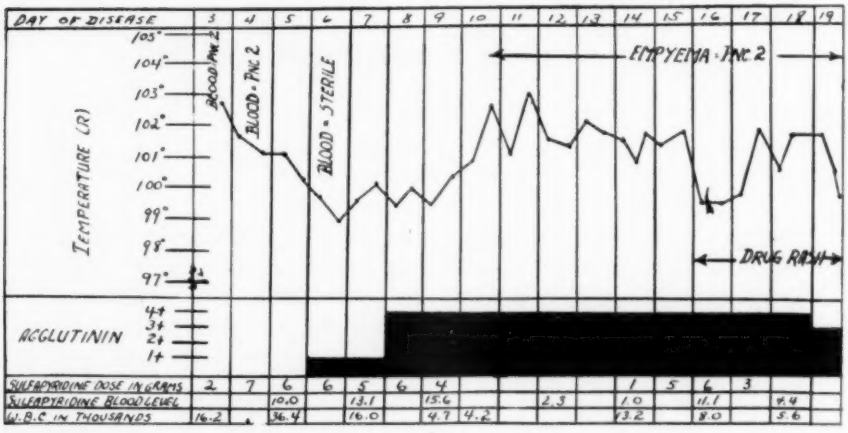
DAY OF DISEASE
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
TEMPERATURE (R)
105° 104° 103° 102° 101° 100° 99° 98° 97°
BLOOD PNC 2
BLOOD - PNC 2
BLOOD - STERILE
EMPYEMA - PNC 2
DRUG RASH
AGGLUTININ
4+ 3+ 2+ 1+
SULFAPYRIDINE DOSE IN GRAMS
2 7 6 6 5 6 4 1 5 6 3
SULFAPYRIDINE BLOOD LEVEL
10.0 13.1 15.4 2.3 1.0 11.1 4.4
W.B.C. IN THOUSANDS
16.2 36.4 16.0 4.7 4.2 13.2 8.0 5.6

CHART 6.—Type II pneumococcic L.L.L. pneumonia with bacteremia and empyema. Septic complication developed in spite of marked agglutination. Sulfapyridine reaction did not influence agglutinin persistence.

(3+) and the patient went on to complete recovery following drainage of the empyema. We believe this case illustrates the failure of sulfapyridine to produce adequate bacteriostasis due to its low concentration in the blood. This occurred in spite of fairly large oral doses. As a result of the patient's poor body defenses (low leukocyte count early in the disease and failure to develop agglutinins until late in the disease) his course was very stormy. After sulfapyridine was discontinued, however, the patient recovered, for by this time he had a good leukocytosis and definitely positive specific agglutinins for Type II pneumococci in his blood.

Chart 6 is of a patient with Type II lobar pneumonia with bacteremia on admission. In spite of a high free sulfapyridine blood concentration, good early leukocytosis, and the development of

strongly positive agglutination for Type II pneumococci on the 8th day of the disease, empyema developed. This may have been a result of the leukopenia (4700) which appeared on the 9th day of the disease necessitating withdrawal of the drug. When the leukocyte count had risen to 13,000 on the 14th day, sulfapyridine was resumed because of the empyema, but again the leukocyte count fell and this time fever and rash also appeared as further signs of a toxic reaction to sulfapyridine. Uneventful recovery followed surgical drainage of the empyema carried out after the sulfapyridine reaction had subsided on the 20th day.

We believe Charts 5 and 6 illustrate that recovery from pneumonia treated with sulfapyridine requires: 1, adequate sulfapyridine concentration in the blood; 2, maintained leukocytosis; and 3, development of active immunity by the patient in response to his infection. When any one of these factors is inadequate, danger of spread, invasion of the blood stream, and septic complications is greatly increased.

Table 1 indicates that in complicated pneumonias a strongly positive agglutination test was not obtained as early in the course of the disease as in uncomplicated pneumonia. In the complicated cases such a reaction was first obtained on an average of 12.5 days after the onset of the illness, while in the uncomplicated cases, agglutinin appeared on an average of 8.3 days after the onset. We feel that failure to develop active immunity (as indicated by the agglutinin test) by the 9th day of illness was a predisposing factor in the development of complications, and that discontinuing sulfapyridine soon after the initial drop in temperature would have been most dangerous in such cases. When possible, sulfapyridine was continued in all our cases until a good agglutination reaction appeared.

TABLE 1.—RELATION OF COMPLICATIONS TO TIME REQUIRED FOR AGGLUTININ FORMATION.

	Day of disease maximum agglutination.	Average of maximum agglutination.	No. of cases.
Uncomplicated cases	8.3	3.1+	27
Complicated cases	12.5	3.5+	23
Total cases	10.4	3.3+	50

Summary. 1. Fifty adult patients with pneumococcic lobar pneumonia treated with sulfapyridine were studied to determine the time at which active immunity first appeared.

2. All patients with proven type-specific pneumococcic pneumonia developed strongly positive agglutinins at some time in the course of their illness.

3. Strong type-specific agglutination occurred in the uncomplicated cases on an average of 8.3 days after the onset of the disease; in complicated cases on an average of 12.5 days.

4. When active immunity did not appear early in the second week of the disease, complications or delay in resolution frequently occurred.

5. Persistence of a strongly positive agglutination for the homologous type pneumococcus was a favorable prognostic sign.

6. Occasionally, empyema developed after a strongly positive agglutination appeared. All such cases, however, had bacteremia on admission and in some cases this persisted for 24 hours or longer after sulfapyridine therapy was begun.

Conclusions. 1. We believe that recovery from pneumonia in patients treated with sulfapyridine requires: 1, adequate blood sulfapyridine concentration; 2, maintained leukocytosis, and 3, development of active immunity by the patient in response to his infection.

2. In uncomplicated pneumococcic pneumonias a safe rule appears to be to continue sulfapyridine therapy at a dosage which will produce a blood level above 4 mg. per 100 cc. until a strongly positive microscopic agglutination test is obtained with the patient's serum against pneumococci of the type with which he is infected. In complicated pneumococcic pneumonias sulfapyridine should be continued, if possible, until the temperature and pulse have returned to normal, even though strongly positive agglutination has occurred prior to that time.

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CONTROL OF URINE REACTION.

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Although there can be no denying that normal kidneys are well equipped to excrete urine at least as acid as pH 5, attempts both medical and otherwise to render this body fluid alkaline are met on every hand. There is, however, growing sentiment against such misdirected effort. Evidence gathered in the laboratory indicates that the kidneys resist interference with the fundamental acid character of the urine and manipulation of its natural variability. Since tampering with urine reaction is undesirable without ade-

quate knowledge of the forces involved, the problem has been approached experimentally with the intention of providing a foundation upon which to base certain phases of medical practice.

Alteration of Urinary Reaction With Diet. Since it is commonly assumed that the intake of food is associated with a urinary shift toward alkalinity, a series of tests was conducted on 6 presumably normal laboratory technicians prior to and shortly after the ingestion of a meal. Four of the subjects in a total of 71 tests revealed urinary pH rise in 9 instances, fall in 59, and no change in 3. The other 2 in 65 experiments showed a rise in 37 instances, drop in 16, and no change in 12. There was no apparent dietary cause for this difference. All subjects were in excellent health. The only obvious

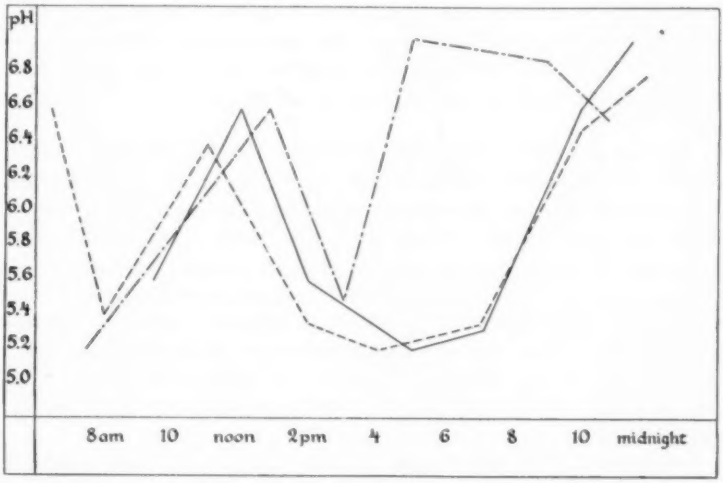

CHART 1.—Urinary pH changes after ingesting one cup of stewed rhubarb. – – – – – – average "normal" curve; ——— after taking rhubarb at 10 A.M.; —·—·—·— after taking rhubarb at 3 P.M.

difference was in temperament. The two subjects with tendency toward alkalinity were emotionally calm and deliberate in their actions in contrast to the others who were more "excitable."

In our experiments we have noted that the urinary reaction responds very quickly to certain foods. This response, however, may be masked by changes in the opposite or in the same direction. Rhubarb, for instance, may or may not materially influence the urinary pH (Chart 1).

The food which has most rapidly alkalinized the urine in our studies has been cantaloupe. Unlike most of the fruits which are ingested as acid although they give an alkaline ash, cantaloupe is close to neutrality, pH 6.17–7.13.[2] No other food was able to raise the pH to such a high level—7.2 to 7.8.

All data herein presented were obtained by comparison with buffer standards and suitable indicators (bromcresol green, pH 4.5–5.4; chlorphenol red, pH 5.2–6.8; phenol red, pH 6.8–8.0). Potentiometric measurements were occasionally undertaken. The results are given in terms of room temperature; correction to 38° C. requires subtraction of approximately 0.2 pH from observations made at 25° C.

The results of 4 consecutive days of an exceedingly strict alkaline-ash diet are depicted in Chart 2. The usual pH curve is unrecognizable the first day, due largely to cantaloupe at breakfast and lunch. On the second day, when the fruits consisted of banana and pear, the outline of the "natural" curve begins to appear. Cantaloupe at lunch on the third day completely distorts the afternoon portion of the curve, but when this fruit was not eaten until the evening meal on the fourth day, the fundamental curve is readily apparent. Neither the dietitian responsible for the food nor the subject were aware of any special alkalinizing effect of cantaloupe before the tests.

It is rather striking that a pH of 4.8 was reached on the second day of this alkalinization régime. On other occasions a tendency for the reaction to shift sharply from either extreme limit toward the other has been noted. When the kidneys are confronted with the necessity of excreting extremely acid or alkaline urine, do they continue longer than excess of acid or base would warrant with a subsequent shift in the opposite direction to achieve metabolic equilibrium? It is not unusual to observe decidedly acid urine in the presence of an alkaline-ash diet. In particular, two dietitians who consistently showed pH 5 on arising continued to do so on an alkaline-ash diet.

Attempts were made to ascertain whether or not base was stored in a practical sense on an alkaline-ash diet or lost on an acidic-ash diet. Before breakfast on the fifth day in each series, each subject took 2- or 5-gram doses of sodium bicarbonate every half hour until the urine turned litmus paper lavender or blue. There was no consistent difference in the amount of bicarbonate required (generally 5–10 gm.) after the two diets. The only one out of 8 subjects who did not need to take any bicarbonate on either diet was the subject shown in Charts 2, 3A, 5, and 6. It is recognized, of course, that this experiment proves very little with regard to loss or storage of base, but it does demonstrate that dietary changes may have an astonishingly small effect upon the reaction of the morning urine.

Of a group tested, 4 typical subjects are presented in Chart 3 to show the difference between a well-balanced diet and one in which the lunch was strictly acidic-ash and the dinner alkaline-ash. Fluid at the luncheon was restricted to 90 cc. of cranberry juice which is one of the most effective means of lowering urinary pH. The

purpose was to obtain an exaggerated response, if possible, by avoiding any upward trend attributable to output of fluid. For a similar reason ingestion of extra fluid was encouraged in the

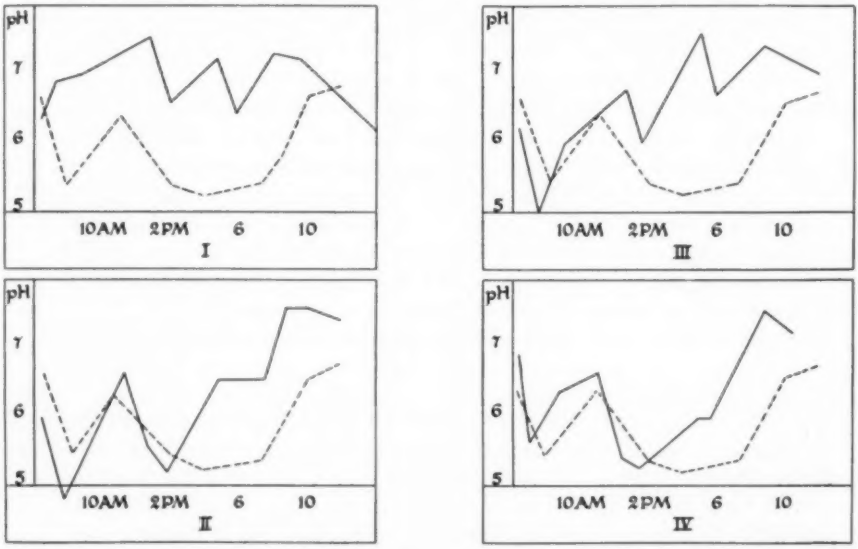

CHART 2.—Urinary pH changes on an alkaline-ash diet. - - - - - - average "normal" curve; ——— changes encountered on specified day of diet.

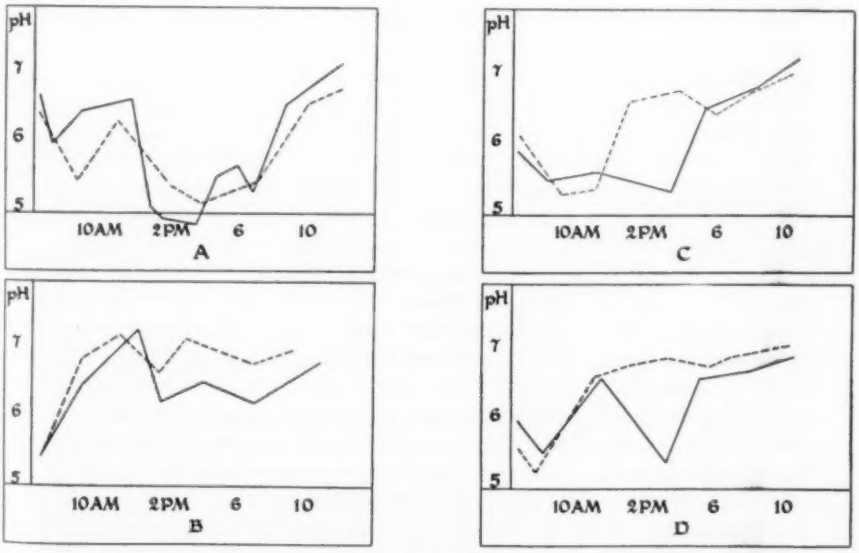

CHART 3.—Urinary pH changes with acidic-ash lunch followed by alkaline-ash dinner. - - - - - - average "normal" curve; ——— response under test conditions.

evening to intensify alkalinization of the urine due to the character of the supper. With 3 of the subjects sharp depression of the pH is seen in the early afternoon, followed by prompt recovery. Subject B, however, shows less acidity but prolongs the depression into the evening. There is no apparent effect of the alkaline-ash supper in any subject.

The curve for Subject A (Chart 3) is not so smooth as the others since specimens were collected more frequently than ordinarily would be voided. It is noteworthy that the drop to unusually low levels is quickly succeeded by an upward trend which overreaches the average curve. The obvious depression at the time of the evening meal is characteristic of this subject on ingesting food. The average curve does not show these depressions since, except for lunch, the major change is in the direction of diminished acidity. Specimens covering the meal period are necessarily small. Even though highly acid, their effect is almost lost in subsequent larger volumes of less acid urine which ordinarily remain in the bladder until micturition occurs.

While it was possible, by taking advantage of the natural trend of the individual, to produce reactions between pH 4.6 and 7.8, these reactions could not be maintained at will with the subject shown in Chart 2. In fact, stubborn efforts at definite acidification or alkalinization were met by erratic and unpredictable changes.

It is not questioned but what 24-hour urine specimens, suitably collected and preserved, would demonstrate a different level on acidic, alkaline, and mixed diets. The reaction of the separately voided specimens presumably provides much more clinically-useful data. We are convinced that any regimen which flattens the daily pH curve, especially in the higher values, is not to be recommended. Many of the recognized end-products of metabolism are acidic and accumulate regardless of diet. Their excretion by means of an acid urine is undoubtedly a normal procedure. Any effort, therefore, to force elaboration of an alkaline urine is bound to be beset with difficulties. It is impossible to excrete a continuously alkaline urine without resorting to large doses of such agents as sodium bicarbonate (excepting those nephritics with fixation at pH 6.8–7.2 and persons with ammoniacal infections).

Alteration of Urinary Reaction With Drugs. Experimentally it has been possible to maintain a pH level of approximately 5 for several days by means of drugs and diet. Subsequently, the pH has risen coincident with an increased output of ammonia, regardless of the diet or further administration of acidifying drugs, thus corroborating the findings of others. A typical case is presented in Chart 4 in which only the pH values are followed.

To conserve space, the observations on this patient are plotted in Chart 4 without reference to time. Since voidings were not frequent, the graph represents a period exceeding a month. To

render mandelic acid therapy for bacilluria (*E. coli*) more effective in this case, acidification had been attempted with a hydrochloric-nitric acid mixture.[4] No satisfactory response was noted until an acidic-ash diet was instituted (point A on the graph). Cranberry juice was introduced on the third day of this regimen, but failure of the pH to fall further led to the suggestion that the mineral acids were responsible. Discontinuance of the HCl-HNO_3 mixture resulted in a sharp drop to pH 5 which was maintained for 5 days. Although there was less acid for excretion the pH fell. A total of 750 cc. of water had been required for administration of the acids.

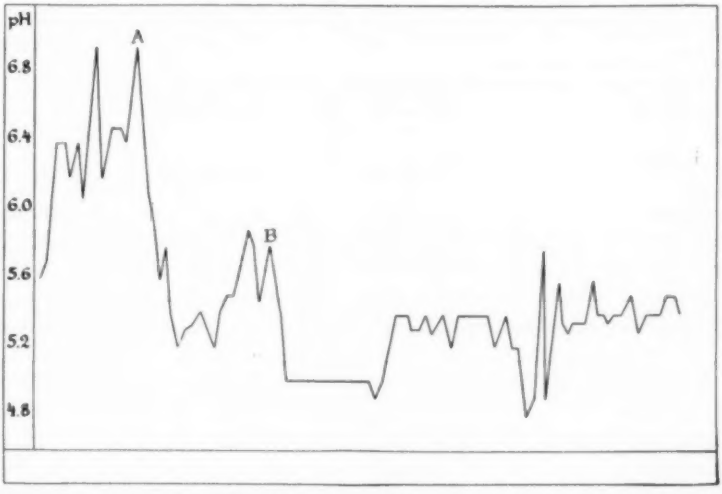

CHART 4.—Urinary pH as affected by drugs and diet. *A*, Institution of acidic-ash diet; *B*, discontinuance of HCl–HNO_3 mixture.

Excretion of this otherwise unnecessary water had interfered with the elaboration of a concentrated, and thus more acid, urine. Water as such was withheld and cranberry, plum and prune juices substituted. An effective acidic-ash diet can often be secured in this manner and yet permit the inclusion of a small serving of one green vegetable, cooked or raw, for lunch or dinner.

After 5 days at pH 5, the urine shifted to a higher level despite little relaxation in the acid therapy. Relative fixation is observed in Chart 4 at a less acid reaction. Greater variability also is seen. If intense acidification is therapeutically desirable, it would seem logical to discontinue the treatment as soon as physiologic adjustment sets in and raises the pH.

In Chart 5 is shown the effect of administering sodium benzoate. It is noteworthy that this drug did not lead to acidification of the urine as seen in the curve itself, although there was prompt excretion of hippuric acid (Table 1). Comparison, however, with the

natural curve of the subject reveals that the usual degree of "alkalinity" failed to materialize. Administration of sodium bicarbonate resulted in a definite rise in pH despite the opposite tendency ordinarily.

TABLE 1.—URINARY CHANGES AFTER ADMINISTRATION OF TEST DRUGS.

Time.	Volume, cc.	pH.	Hippuric acid as benzoic, gm.
9 A.M.	40	5.0	
9.05 A.M.	*Administration of benzoic acid (5.8 gm. in 130 cc. of water)*		
10 A.M.	67	5.7	0.89
11.15 A.M.	116	5.8	1.40
NOON	66	5.4	1.67
1.05 P.M.	57	5.2	0.88
			4.84 (total)
(No lunch permitted)			
1.10 P.M.	*Administration of $NaHCO_3$ (4 gm. in 200 cc. of water)*		
3 P.M.	50	5.4	
4 P.M.	15	6.2	
5 P.M.	15	7.2	
5.25 P.M.	8	6.9	

Chart 6 shows the same subject under mandelic acid. Although this drug did not affect the morning "alkaline" peak, it had a slight lowering effect during the afternoon when taken in conjunction with a substantially acidic-ash lunch. Without provocation, however, the pH rose to an unusually high level after an early dinner (mixed diet)—which is an instance of behavior previously mentioned.

Predetermining the Reaction. It is often taken for granted that the reaction of the urine can be altered at will. In 100 experiments upon one subject it was attempted to predict the urinary pH by controlling the supposed factors in its production. The majority were complete failures. The diet was planned to force the excretion of highly acid or strongly alkaline urine without much success. Not until it was recognized that there was a fundamental acid-base rhythm was it possible to shift the pH in the desired direction, and then only by taking advantage of the rhythm. All efforts to reach a very low pH were unsuccessful except those which coincided with the lowest level of the "natural" curve, that is, in the early afternoon. Likewise, the highest values for pH could be obtained only in coincidence with the morning or evening peak of diminished acidity.

The normal individual experiences a variation in urinary pH such that definite decrease in acidity occurs at some time between 9 A.M. and midnight. The urine may or may not become actually alkaline. The time of the peak of diminished acidity is more or less characteristic of the individual. Likewise, the entire curve for 24 hours tends to assume a similar pattern day after day—so much so that in a limited group, once the trend is known, it is possible to identify unlabelled curves. For example, 6 dietitians living under the same roof and partaking of the same general diet presented 6 different

curves which persisted in spite of deliberate alteration in the acid-base residue of the diet. Again, upon a group of inmates of a prison hospital, curves were obtained on repeated testing which were consistently alike for the individual, yet different from each other. Likewise, a group of technicians and students on 3-day test periods

CHART 5.

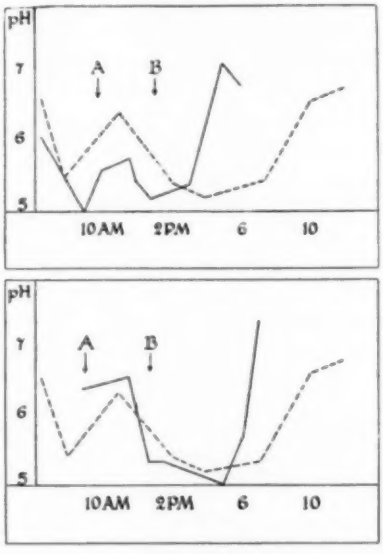

CHART 6.

CHART 5.—Urinary pH changes after test drugs. *A*, 5.8 gm. of sodium benzoate; *B*, 4 gm. of sodium bicarbonate (see also Table 1).

CHART 6.—Urinary pH changes after ammonium mandelate. *A* and *B*, 0.5 gm. doses.

presented striking similarity for a given subject and dissimilarity with others in the group. Typical curves are shown in Chart 7.

Our observations convince us of the presence of a natural rhythm characteristic of the individual which is the result of manifold factors and which tends to manifest itself despite efforts to alter it. Although this point of view has been given little place in the literature, it has not escaped the notice of others. Particular reference should be made to Obermer of London[7] who, on examination of our individual curves, not only confirmed our impressions but went so far as to suggest that the urinary pH curve for the 24-hour period was a physiologic characteristic comparable, after a chemical fashion, with finger prints.

The curve will not invariably follow the same pattern under all conditions (therein lies its usefulness), but *this basic variation will impose itself upon accidentally or intentionally produced urinary changes.* Neglect of this fact or ignorance regarding the form of the

individual curve can only lead to conclusions which, at best, are not warranted and which, at worst, are wholly fallacious.

It is not intended to create the impression that the urinary pH curve is so uniform that its similarity is apparent to the most casual observer—quite the contrary. If specimens are obtained frequently, minor variations may obscure the general trend, but when such

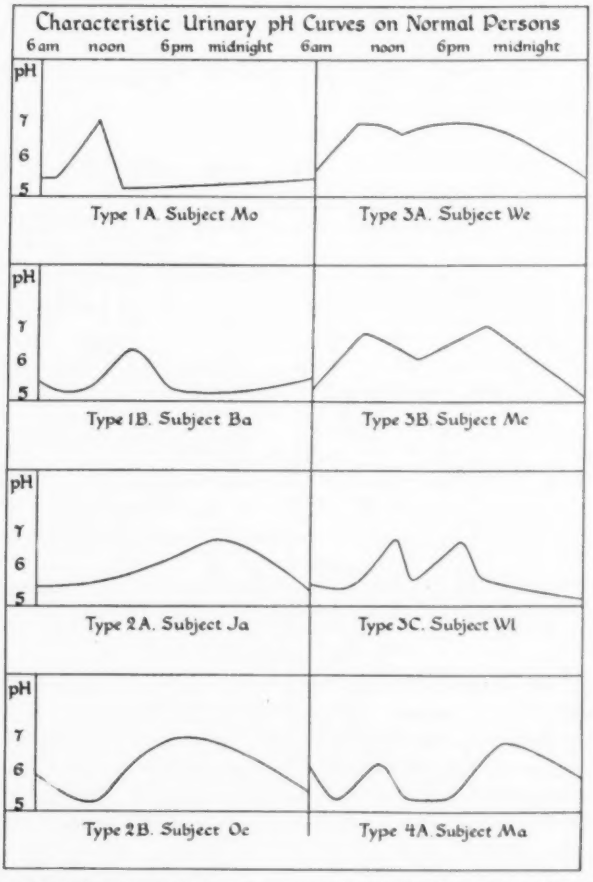

CHART 7.—Typical urinary pH curves representing the fundamental acid-base rhythm of various subjects.

curves are superimposed upon others from the same person and viewed by transmitted light, the fundamental change in each is more evident.

Some subjects show marked persistence in the urinary pH curve while others deviate on comparatively slight provocation. The greatest variability was shown in the youngest group studied: 10

college undergraduates. It would appear that capricious eating habits, the conflict and strain attendant upon assignments and quizzes, "dates" and general restlessness contribute much to the changeableness of the urinary curves. It must be admitted, however, that one of the most consistent curves encountered was in this group; for the 12 consecutive days of the test this girl showed no variation in the form of the curve.

The present state of our knowledge does not permit a complete listing of all the factors which enter into the composite urinary pH curve. It is generally assumed that the chief factor influencing the excretion of acid by the kidney is the elaboration of HCl in the stomach[5] although experimental evidence is far from substantiating this claim. Other factors usually stressed include fluid intake, diet, and changes in the respiratory center.[3] Alteration of the normal course of events, such as development of a cold or the taking of an effective saline cathartic, may manifest itself in conspicuous fashion in the urinary pH curve. Although hyperventilation *per se* leads to increased alkalinity, exercise intensifies the acidity of the urine. According to Obermer:[7] "Insofar as it is possible to correlate two independent variables without taking a host of others into consideration, fatigue tends to make the pH more alkaline, rather than more acid." The behavior of the thyroid gland may be an important means of altering urinary reaction. Possibly emotional and mental states play a far greater rôle than is realized. Numerous illustrations could be culled from our studies, but two will suffice: 1, A student who presented an extraordinarily flat and highly acid curve day after day excreted decidedly alkaline urine when she received news of serious illness at home; 2, a patient who showed unexpected departure from his usual curve was startled by being asked what happened at a specified hour; he had had occasion to reprimand his children at that time.

Among readily determinable factors which affect the urine reaction, availability of water for excretion is noteworthy. A series of 97 tests upon urine obtained without motive is described in Table 2.

TABLE 2.—RELATIONSHIP BETWEEN RATE OF URINE FLOW AND pH.

No. of observations.	Urine flow.	pH range.
43	1 cc. per minute or less	4.8–5.8
23	1 cc. per minute or less	6.0–7.0
6	1.1–3.8 cc. per minute	5.3–5.7
25	1.1–3.8 cc. per minute	6.0–7.3

From this group are excluded all first morning specimens since urine is normally formed at a diminished rate during sleep at a reaction which possibly is somewhat typical of the individual. Although apparently the majority of normal persons excrete a decidedly acid morning urine, such a finding is unusual for this subject (Chart 2). The 13 night specimens in the series from which

these data are drawn were all below 1 cc. per minute, yet 9 of them varied from pH 6.5 to 6.9, the remaining 4 between 6.0 and 6.4.

Water ingested and not needed by the normal body is promptly (depending on the time of day) excreted in a dilute urine, the pH drifting upward. Similarly, lack of water for excretion is generally associated with highly acid urine. By experimental planning, however, the urine was forced in seven instances to a pH of 7.2–7.8 when the volume amounted to 1 cc. per minute or less. On the other hand, diuresis was produced with grape juice (500 cc. diluted with water to 1 liter and ingested within 90 minutes) yet the pH remained low, the results being given in Table 3. Cranberry, plum, and prune juices also tend to drive the pH downward while the rate of urine formation increases.

TABLE 3.—EFFECT OF INGESTING AN EXCESSIVE AMOUNT OF GRAPE JUICE.

Urine flow.	pH.
1.2 cc. per minute	5.3
2.5	5.6
3.4	5.7
6.2	5.7
6.5	5.4
7.0	5.0
9.5	5.7

The tendency for volume increase to be associated with elevation of pH is frequently ignored. When 500 cc. of water are given in lieu of breakfast for the production of an "alkaline tide," the diminished urinary acidity often encountered may merely reflect the increased output of fluid. Conversely, if the amount of water eliminated is small, the pH may remain at a low level and a "tide" be declared absent and attributed to lack of gastric acid! Hubbard *et al.*[5] report but do not consider the urinary volumes when investigating pH variations with and without breakfast, but the differences in fluid output are as striking as the changes in pH.

The tense attitude assumed by a runner about to start a race causes a drop in urine volume (MacKeith *et al.*, 1924). Wilson[10] tried to eliminate the decrease in urine volume by water drinking, but frequently without success. Even with 200 cc. of water every 30 minutes for 2 hours preceding and extending through the period of exercise, the urine volume still fell to less than one-seventh that of the fore-period. After 1 to 2 minutes of strenuous exercise, the diminished water output was accompanied by increase in hydrogen-ion concentration, titratable acidity, and ammonia output. The urine was collected at 10-minute intervals or less. The maximum change was reached within half an hour, followed by return to "normal" in 40 to 90 minutes.

The rate of water excretion varies throughout the 24 hours. Simpson and Wells[9] attempted with dogs to get a uniform excretion but failed. Regardless of the intake of 100 to 200 cc. of fluid hourly,

Simpson[8] obtained a negative water balance during part of the day and water retention at night during sleep. The acid retention period ended about 7 A.M., the subsequent polyuria being accompanied by relatively high pH. A marked decrease in urinary volume was encountered by Simpson between 2 and 6 P.M. and a second maximum between 6 and 9 P.M. According to Best and Taylor[1] the urine volume during the day (8.30 A.M. to 8.30 P.M.) is 2 to 4 times that of the night. The ratio holds, even if the quantity of fluid taken during both periods is the same.

Pathologic Fixation of Urinary pH. Efforts to control the reaction of the urine are frequently disappointing. In normal individuals it is often surprisingly difficult to fix the pH by diet or drugs. It is equally difficult to alter the pH when disease fixes it. Attempts to do so are not necessarily in the best interests of the patient. Although highly acid urine may be seen early in nephritis, progressive impairment gradually raises the level of fixation to neutrality foreshadowing the fatal termination of the disease. Unusual acidity has been noted[6] in cardiac decompensation when the urine output is low; release of the edema fluid with consequent upward shift in the pH occurs as the patient improves. We have observed fixation of pH below 5 in cardiacs.

The statistical study of Ziegler and Brice[11] warrants the conclusion that "the ability of the kidney to excrete solids and to concentrate the urine is greater when the urine is acid than when it is alkaline or neutral." According to these investigators, acid urines show fewer abnormal findings than those which are alkaline or neutral and emphasis is placed upon the undeniable fact that the human kidney is phylogenetically adapted to excrete an acid urine.

Summary. 1. The urinary pH cannot be consistently changed at will without regard for its natural trend.

2. The acidifying or alkalinizing effect of test substances cannot be judged solely by the urinary pH observed. Comparison with the fundamental or natural curve is necessary.

3. The natural acid-base curve can be distorted by dietary factors with variable ease in different subjects.

4. The determination of urinary pH following meals is of no practical clinical value.

5. It has not been possible by dietary measures to produce continuously alkaline urine.

6. Temporary elevation of urinary pH is most readily secured with cantaloupe.

7. The easiest means of maintaining acid urine in the normal individual is the substitution of cranberry juice for water as such in the diet.

8. The effective action of acidifying drugs is conditioned by the amount of water simultaneously claiming excretion.

9. Although concentration of urine is regularly associated with

increasing acidity and dilution with increasing alkalinity, the normal kidney can excrete a highly acid dilute urine and a definitely alkaline concentrated urine. The elimination of water is not constant throughout the day, thus influencing the urinary pH.

10. Emotional and mental states demonstrably affect urinary pH.

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EFFECT OF NICOTINIC ACID ON PERIPHERAL BLOOD FLOW IN MAN.*

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In a number of the reports upon the use of nicotinic acid in the treatment of pellagra[5,7,8] the appearance of such cutaneous manifestations as burning, itching, flushing of the face and trunk, and a feeling of warmth has been noted. These symptoms generally were present following the administration of at least 200 mg. of the drug orally or 5 to 25 mg. intravenously. Coincident with the onset of the above symptoms, Spies and his associates[3,7] found an increase in skin temperature which was most marked over the ears, face and neck, less pronounced over the trunk and least over the extremities. Papkin[6] has recently reported rather inconstant surface temperature readings following the administration of smaller quantities of the drug. Since these reactions are obviously vascular in nature, it was considered of interest to investigate the influence of nicotinic acid on peripheral blood flow by means of plethysmographic studies.

* Aided by the Samuel and Regina Kuhn Fund and a grant from the Dazian Foundation for Medical Research.

Method. Twenty-eight experiments were performed on 15 adult subjects who had been maintained on well balanced diets. Nicotinic acid was given by mouth except in 5 instances in which it was administered intravenously. The plethysmographs and technique utilized were similar in all respects to those described previously by one of us.[2a,b,4] Generally a contralateral hand and forearm, or forearm and leg, were studied simultaneously. The room temperature, except where otherwise indicated, was between 25 and 27° C. and the bath temperature (*i. e.*, temperature of water in the plethysmograph) was 32° C. All readings were calculated as cc. of blood flow per minute per 100 cc. of limb volume. After a control level was determined over a period of 30 minutes, nicotinic acid was administered and blood flow records were obtained (from 5 to 10 in each period) at approximately 15-minute intervals for the subsequent 70 to 150 minutes. The onset and duration of the various symptoms were noted and blood pressure and pulse rate were recorded at intervals during the experiment. In six experiments, skin temperature readings were obtained by means of a Tycos dermatherm.

As reported by previous investigators,[7] the oral dosage of the drug necessary to produce symptoms varied markedly in different subjects and even in the same subject on different occasions. More consistent results were obtained if the procedure was performed in the post-absorptive period; the effective oral dosage under these circumstances ranged between 100 and 300 mg. On the 5 occasions in which the drug was injected intravenously, 20 to 25 mg. were used, in each instance definite symptoms being elicited.

Results. *Effect Upon the Hand.* With oral administration, a significant increase in blood flow to the hand was noted in 16 out of 19 instances (Table 1). The maximal flow attained in these experiments averaged 2.2 times the control level. In one of the remaining cases (Expt. 8) there was only a slight increase, but in this experiment the initial flow was much above the normal level due to a high room temperature (32° C.). In two instances (Expts. 17 and 18) in which no change in hand flow was noted, a significant increase in forearm flow was present. The maximal effect in the hand occurred in from 15 to 155 minutes following the administration of the drug. The duration of the increased flow over control readings averaged 75 minutes, the experiments being frequently terminated before the control level had again been reached (Chart 1). In a number of instances, a transient decrease in blood flow occurred from 10 to 70 minutes after administration; generally it preceded the increase.

In 1 of 3 experiments in which nicotinic acid was injected intravenously, a transient rise in flow to the hand (1.3 times) was noted about 4½ minutes after administration (Expt. 25). However, in this instance as well as in the other 2 experiments, the predominating effect was a decrease in flow to the hand despite the fact that in each case there was an increase in the forearm or leg studied simultaneously.

Effect Upon the Forearm. With oral administration of nicotinic acid, a significant increase in blood flow to the forearm was noted in

15 out of 19 instances (Table 1). The maximal flow attained in these experiments averaged 2.5 times the control level. Of the remaining cases, in one (Expt. 6) there was a slight rise and in another (Expt. 21) a significant but transient rise. In two (Expts. 12 and 20) in

TABLE 1.—EFFECT OF NICOTINIC ACID ON PERIPHERAL BLOOD FLOW.

A. *Oral Route.*

Subject.	Experiment.	Dosage (mg.).	Extremity.	Control blood flow.	After nicotinic acid.			Extremity.	Control blood flow.	After nicotinic acid.		
					Maximal increase.	Time of maximal effect (min.).	Duration of increase in flow (min.).			Maximal increase.	Time of maximal effect (min.).	Duration of increase in flow (min.).
M. F.	1	100	H	4.1	11.7	90	50–110	F	1.2	2.7	110	10–110
D. F.	2	100	H	7.1	14.1	40	20–70	F	2.1	4.2	60	20–70
D. A.	3	100	H	8.9	16.0	90	60–100	F	2.2	5.4	100	75–100
	4	150	H	3.2	11.7	155	40–155	F	1.0	1.7	150	135–150
	5	225	H	8.1	13.0	70	40–90	F	1.4	4.2	40	17–80
	6	275	L	0.8	1.0	54	54–80	F	1.9	2.3	25	15–60
	7	300	H	3.2	6.5	45	35–75	L	0.9	0.9	..	....
K. K.	8	100	H	21.6	26.6	30	30–60	F	1.6	6.7	60	20–90
	9	200	L	1.1	2.0	70	20–90	F	0.8	3.3	60	30–90
	10	100	H	5.7	13.7	120	90–120	F	1.1	2.9	120	70–120
	11	100	H	2.7	17.3	150	30–150	F	1.1	2.1	90	60–150
L. S.	12	100	H	6.3	13.4	140	80–150	F	2.9	2.9	..	....
	13	200	L	0.9	1.1	60	30–70	F	1.9	4.2	50	30–110
C. H.	14	200	H	3.0	8.0	120	35–120	F	1.0	1.83	35	20–120
M. B.	15	150	H	11.6	16.3	15	5–30	F	1.2	2.1	60	15–80
D. D.	16	225	H	8.9	16.6	30	10–80	L	3.9	4.3	80	30–80
D. C.	17	225	H	14.7	14.9	..	....	F	2.7	4.1	18	18–80
J. N.	18	200	H	7.0	7.0	..	....	F	1.7	2.7	60	30–160
G. G.	19	150	L	2.4	2.8	30	10–120					
	20	175	H	7.7	13.6	70	30–100	F	3.4	3.4	..	....
P. A.	21	175	H	3.5	8.9	120	30–120	F	1.5	2.7	20	10–20
M. G.	22	200	H	1.3	3.1	57	30–84	L	0.8	1.1	70	60–80
D. S.	23	225	H	9.3	12.8	22	15–65	F	2.6	9.6	56	12–75

B. *Intravenous Route.*

J. N.	24	25	H	10.6	9.7	..	....	F	1.4	4.0	5	2–110
	25	25	H	10.1	13.1	4½	1–12	L	3.6	5.6	4½	....
F. S.	26	20	H	13.8	7.7	..	....	F	1.05	3.7	30	5–60
K. K.	27	20	L	0.8	1.4	50	8–80	F	1.3	2.4	32	8–80
M. G.	28	25	L	1.8	1.7	..	....	F	1.5	2.8	2	2–45

All blood flow figures are in cc. per min. per 100 cc. of limb volume.
H = hand; L = leg; F = forearm.

which no change in blood flow was observed in the forearm, a significant increase was present in the hand. The maximal effect in the forearm occurred in from 20 to 150 minutes (average 70 minutes) after the administration of the drug; the duration of increase over control level averaged 66 minutes.

In 4 instances in which the effect of intravenous injection of the drug was studied, a significant increase consistently took place in the forearm. The maximal flow attained averaged 2.5 times the control level, the augmentation continuing for from 43 to 108 minutes after administration.

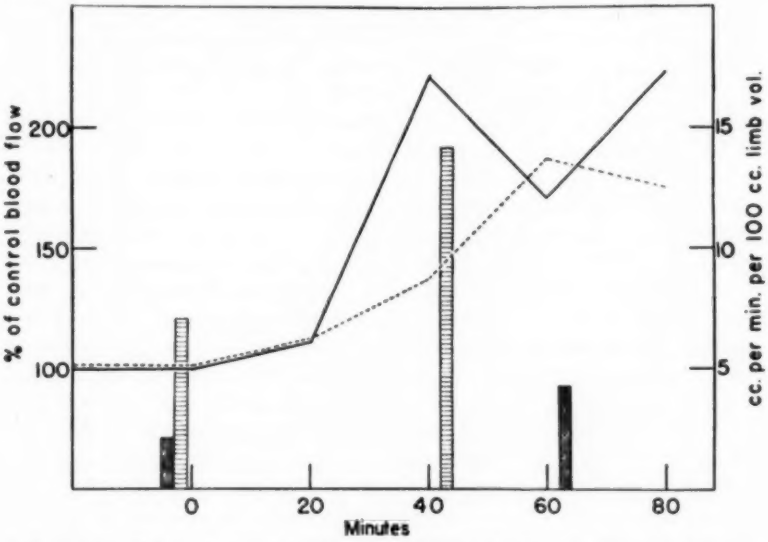

CHART 1.—Effect of the oral administration of 100 mg. of nicotinic acid upon blood flow in hand (solid line) and forearm (dotted line) in subject D. F. (Expt. 2). The lines represent percentage change in flow as compared with the controls. Horizontal-lined column: hand blood flow in cc. per minute per 100 cc. limb vol. Cross-hatched column: forearm blood flow in cc. per minute per 100 cc. limb vol. Bath temp. 32° C.; room temp. 26° C.

Effect Upon the Leg. With oral administration of nicotinic acid, only a slight or no increase in blood flow to the leg was noted in the seven subjects thus tested. The maximal flow attained in these experiments averaged 1.3 times the control level (Table 1). Generally, the contralateral forearm, tested simultaneously, showed a significant increase in flow. The intravenous injection of the drug, studied in three instances, resulted in an increase of blood flow to the leg of 1.7 and 1.5 times the control level in 2 experiments, and no effect in the remaining one.

Effect Upon Blood Pressure and Pulse. For the most part, blood pressure and pulse rate were very little affected by either the oral or intravenous administration of nicotinic acid. In 4 instances, there was an average rise of 4 mm. in systolic pressure, in 6 an average fall of 6 mm., and in 4 no change. In 5 instances there was an average rise of 5 mm. in diastolic pressure, in 2 an average drop of 5 mm., and in 7 no change. At the time when the maximal increase in blood flow to the extremities was noted, the blood pressure

was generally at approximately the same level as the control readings. The pulse rate change varied from an average increase of 3 beats per minute to an average decrease of 10 beats.

Effect Upon Skin Temperature. In 6 experiments, skin temperature readings were obtained from the forehead and the extremities simultaneously with blood flow determinations. The changes in the forehead showed no consistent trend and in no case were they significant. Likewise with the forearm, very little alteration in skin temperature was encountered, despite the fact that in this site definite increases in blood flow were consistently noted. The same findings were also present for the hand.

Cutaneous Manifestations. A correlation between the degree and intensity of flushing of the face and the magnitude of the change in peripheral blood flow to the hand and forearm could generally be noted. With oral administration the only exceptions consisted of one instance (Expt. 17) in which a moderate flushing of the face was present, but no change in blood flow to the hand (that to the forearm being increased), and of another case (Expt. 21) in which no symptoms were observed, but still there was an increase in flow to both hand and forearm (the effect in the latter being transient). Of the remaining 21 instances, in 18 there was a definite flushing present together with a significant increase in flow to the extremities, while in the other 3, minor symptoms were observed and an increase in flow was limited to only one of the two limbs studied (Expts. 12, 18 and 20). In 7 experiments on 4 subjects (not included in the table) neither symptoms nor changes in blood flow in the hand or forearm were noted following the oral administration of the nicotinic acid; in each instance the drug was taken shortly after a meal. When 2 of these subjects were retested using the intravenous route, significant changes in blood flow, accompanied by definite generalized flushing, were elicited. Conversely, in one subject, intravenous injection of 20 mg. of nicotinic acid elicited no or very slight symptoms and no change in blood flow, while oral administration produced definite peripheral vascular responses.

Besides the flushing of the face, which generally was the predominating symptom, in a number of instances the trunk, abdomen and extremities were also involved in the response. When flushing of the limbs was present, it was usually noticed some time after the face and neck were affected, and similarly it remained for some time after the flush had disappeared from the latter sites. Accompanying the flushing were the feeling of general body warmth, itching and stiffness of the face, thumping in the head, slight headache and in 3 instances, pain in the abdomen which was transient. These symptoms generally appeared within 10 to 45 minutes after the oral administration of the drug and within 1 to 3 minutes when the intravenous route was used, most of them persisting for from 40 to 70 minutes. In the case of the intravenous administration, a

transient metallic taste was experienced by some of the subjects within 10 seconds after injection. These findings are for the most part in accord with those reported by others.[7] In no experiment were toxic symptoms encountered with the dosage used in the study.

Discussion. On the basis of the above data, it can be stated that the administration of nicotinic acid to subjects on well balanced diets results in a significant increase in blood flow to the hand and forearm. Since these changes in peripheral flow are not accompanied by any definite or consistent alterations in blood pressure or pulse, the probability exists that the increase in flow is due to local changes in the blood-vessels at the periphery rather than to an increase in cardiac output. The finding of an increase in total blood flow through the forearm and the hand without any concomitant rise in skin temperature in these sites suggests that the predominating effect is not upon the cutaneous vessels but rather upon those in the muscles. These observations indicate therefore that the absence of a significant change in skin temperature does not necessarily imply that there has been no alteration in total blood flow to an extremity. Such an assumption has recently been made in a study upon the peripheral vascular effects of nicotinic acid.[6]

Judging from the results obtained in those individuals in whom repeated tests were made and also in one subject who received daily doses of nicotinic acid for about 3 weeks (not included in Table 1), it appears that a tolerance for this drug is not developed. However, as mentioned before, the dosage necessary to produce symptoms and changes in blood flow varies even in the same subject on different occasions. The explanation for the more consistent results obtained when the drug was given on an empty stomach may be that a certain concentration in the body is necessary in order to elicit the peripheral vascular responses. Probably the absorption of the drug shortly after a meal is too slow for the establishment of the proper blood level. Inasmuch as changes in blood flow were produced by oral administration, there is no advantage to the intravenous route, especially since on the three occasions in which the hand was studied under the latter conditions, a decrease in flow to this portion of the extremity was observed simultaneously with an increase to the forearm or leg. Since it has been shown that the blood-vessels in the hand respond by marked constriction to various types of stimuli,[1] it is likely that the fear and apprehension, associated with the procedure of intravenous injection, were responsible for these results.

In view of the fact, therefore, that significant increases in blood flow to the hand and forearm can be produced by the oral administration of therapeutic amounts of nicotinic acid, this drug may have a place in the treatment of conditions in which an increased blood supply to the extremities is desired.

Summary. The peripheral vascular effects of nicotinic acid were studied by means of the plethysmographic method in a series of 15 subjects maintained on well balanced diets. It was found that a significant increase in blood flow was generally elicited in the hand and forearm, with only a slight increase in the leg.

Since the changes in peripheral circulation were not accompanied by any definite or consistent alteration in blood pressure or pulse rate, it is probable that the effect was due to local changes in the blood-vessels rather than to an increase in cardiac output.

The possibility is therefore offered that nicotinic acid may be of use in the treatment of extremities with diminished blood supply.

The authors wish to express their appreciation to Dr. Moses Salzer, at whose suggestion this study was undertaken, and to Dr. Harry Salzer, for his coöperation in supplying subjects.

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THE UTILIZATION OF VITAMIN A ADDED TO MINERAL OIL.

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One of the major objections to the use of mineral oil as a laxative or as a substitute for absorbable fat in reduction diets, is due to the preferential solubility of carotene in it and the subsequent loss of the carotene with the excretion of the mineral oil in the stool. This fact has been demonstrated by animal experiments[1,4,6–8,10] and also by studies on human subjects.[2,3] It makes little difference whether the mineral oil is plain or one of the emulsified types whose liquid petrolatum content is less. The preferential solubility of carotene in mineral oil is so great that at body temperature 100 cc. of plain mineral oil could hold as many as 466,666 units of vitamin A in the form of carotene.[2] Amounts of mineral oil as small as 15 or 30 cc. would still be able to remove all of the carotene from a normal diet if the oil came in intimate contact with the food substances containing the carotene.

An attempt was made by one of us[2] to alleviate this objection to the use of mineral oil by presaturating it with carotene and then giving it to a group of patients. Although the precarotene saturated oil protected the ingested carotene from solubility in the mineral oil the compound was grossly changed in color and taste. The cost of adding sufficient carotene to saturate mineral oil at body temperature would be prohibitive.

In one of the early experiments done by Moness and Christiansen[8] on this subject, it was shown that the utilization of vitamin A was not altered by mineral oil if the vitamin A was given as cod liver oil. At this time, however, it was not known that carotene and vitamin A were different substances and the initial workers[1,4] had used butter fat as a source of vitamin A rather than cod liver oil. After Moore[9] reported that vitamin A and carotene were different substances Dutcher, Harris, Hartzler and Guerrant[5] showed that carotene in corn oil was not utilized in the presence of mineral oil but a carefully prepared pigment-free vitamin A concentrate was utilized readily when fed with mineral oil.

This difference in the effect of mineral oil on the preferential solubility of carotene and of vitamin A in oil suggested to us that it might be possible to make a mixture of mineral oil and vitamin A which could be fed to vitamin A deficient rats and by this method to determine whether the animals could remove any, a part, or all of the vitamin A from the mineral oil.

Method. Four groups of rats, totalling 30 in number and representing four litters, varying in ages from 28 to 32 days, were put on the following vitamin A depletion diet:[6]

Food substance.	% by weight.	% calories.
Casein, extracted	18	16
Starch (Kingsford's)	63	55
Salts (Osborne and Mendel, 1919)	4	
Hydrogenated vegetable oil (Crisco)	15	29
Yeast, 400 mg. daily.		

Five of the rats, chosen from each of the four litters employed and represented as Group I, were used as controls and remained on this diet throughout the depletion period and until death.

Eight rats comprising Group II were allowed to remain on the diet until the signs of depletion occurred by loss of weight or xerophthalmia or both. Four were then given 0.5 cc. of mineral oil containing 2 units of vitamin A daily and 4 were given 0.5 cc. of cottonseed oil containing 2 units of vitamin A daily.

Group III consisted of 10 rats that were given the depletion diet until signs of vitamin A deficiency occurred. Four were then given 4 units of vitamin in 0.5 cc. of cottonseed oil daily and 6 were given 4 units of vitamin A in 0.5 cc. of mineral oil daily.

Group IV consisted of 7 animals. They followed the same regimen as Groups II and III except that 3 received 6 units daily of vitamin A in 0.5 cc. of cottonseed oil, and 4 received 6 units daily of vitamin A in 0.5 cc. mineral oil.

The source of vitamin A was a fish liver oil concentrate containing 190,000 units of vitamin A in each gram of oil. The concentrated fish liver oil was diluted with mineral oil and cottonseed oil until stock solutions were obtained containing 2, 4, and 6 units of vitamin A in each 0.5 cc. of mineral oil and cottonseed oil. The stock solutions of both were kept in the ice box except when being used.

The 0.5 cc. doses of cotton seed oil with vitamin A and mineral oil with vitamin A were administered to the rats by adding the mixture to the yeast powder and making a soft pill out of it. The rats ate this mixture readily and usually at once.

The stools of the rats receiving cottonseed oil were normal. The rats receiving mineral oil had large, greasy and more numerous stools.

All animals, except the control group, were continued for 70 days each on cottonseed oil or mineral oil to which was added vitamin A after signs of depletion had appeared.

Experimental Data. It will be seen in Chart 1 that the 5 control animals began to show definite weight changes in from 30 to 50 days after they began eating the experimental diet and xerophthalmia developed, as indicated by a circle with a cross on it, after 45 to 75 days on the diet. Death occurred from 65 to 129 days after the diet was begun as indicated by a cross on the chart.

The animals that received a daily dose of 0.5 cc. of cottonseed oil with 2 units of vitamin A slowly resumed growth. This supplement was begun when depletion of vitamin A was evident, and it is indicated by an arrow on the chart. Rat 5 grew poorly and lost some weight near the end of the experiment. Rat 31 also lost weight and had a reappearance of xerophthalmia near the conclusion of the experiment.

Chart 1 also shows the effect of 2 units of vitamin A dissolved in a daily dose of 0.5 cc. of mineral oil begun after depletion was apparent by a cessation of growth. In this group of animals growth resumption was at least as good when mineral oil carries vitamin A, as when it is present in cottonseed oil. The growth of the animals following the administration of vitamin A in mineral oil, shows that they are able to extract the vitamin A from the mineral oil.

When this experiment was begun it was not known whether the experimental animals could remove any of the vitamin A from the mineral oil or whether they might be able to remove only a portion of it. Since 2 units of vitamin A are sufficient only for maintenance and not for normal growth, it seemed necessary to have comparative growth curves of rats on larger doses of vitamin A, both in an absorbable medium and in the unabsorbable mineral oil. Charts 2 and 3 represent the effect on growth of daily doses of 4 and 6 units of vitamin A in 0.5 cc. of cottonseed oil on rats previously depleted by a deficient diet compared with the effects on growth of daily doses of 4 and 6 units of vitamin A in 0.5 cc. of mineral oil on rats depleted of vitamin A. A small chart of the control animals is included for comparison. It is again apparent that rats can quantitatively extract the vitamin A from mineral oil if growth increases

are used as indices. Growth, during the administration of vitamin A in mineral oil, is as good as growth with vitamin A in cottonseed oil.

Chart 4 shows that 2 units of vitamin A daily give poorer growth after depletion than 4 units daily. There is no real difference in growth resumption on 4 and 6 units of vitamin A daily so that the optimum amount of vitamin A for good growth after depletion is no more than 4 units but is more than 2 units of our concentrate of fish liver oils. With the exception of one animal, Rat 28, that grew unusually well, the growth curves after depletion of vitamin A are as good, when a medium of unabsorbable mineral oil is used, as when an absorbable oil such as cottonseed oil is used.

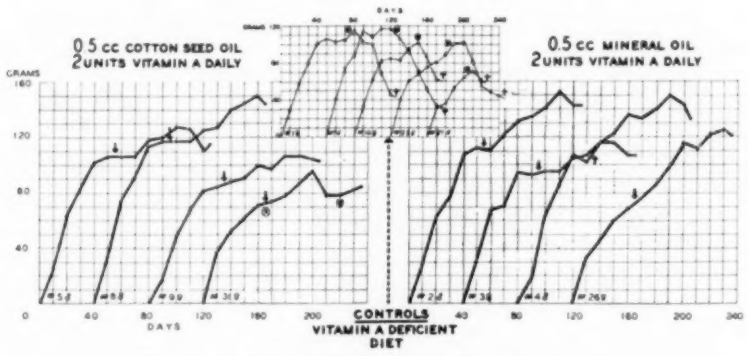

CHART 1.—GROWTH CURVES AND XEROPHTHALMIA.

The growth curves and time of development of xerophthalmia of the control animals on vitamin A depletion diets are illustrated in the smaller upper middle part of the chart. The left chart shows first the growth curves of animals on the depletion diets and then the effect of daily amounts of 0.5 cc. of cottonseed oil and 2 units of vitamin A begun when vitamin A depletion had occurred. The chart on the right illustrates the growth curves on another group of animals on the same depletion diets but differs in that mineral oil with 2 units of vitamin A were given in 0.5 cc. doses daily instead of cottonseed oil. ⊕, xerophthalmia; †, death; ↓, day when cottonseed oil with vitamin A or mineral with vitamin A was begun.

Discussion. From the experiments herein described it seems that one of the major objections to the use of mineral oil as a cathartic can be controlled by making a mixture of vitamin A and mineral oil, or by giving vitamin A with mineral oil. Although carotene would still be lost by its preferential solubility in mineral oil, enough vitamin A could be taken with or put in the mineral oil to give back to the body as much or more vitamin A than the mineral oil would remove as carotene from the food. This could be done by either taking enough fish liver oil with each dose of mineral oil to supply the daily requirement of vitamin A or by making a mixture of mineral oil that would have from 3000 to 6000 units of vitamin A in each average dose. The resulting mixture would have the advantage of being colorless, and could be made practically tasteless and odorless.

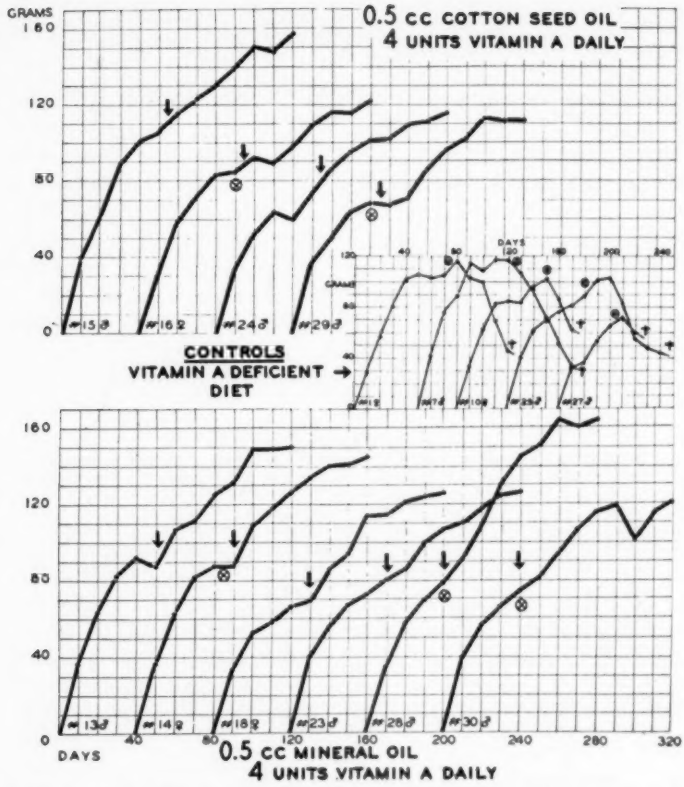

CHART 2.—The effect of 4 units of vitamin A. This was given daily in either 0.5 cc. of cottonseed oil or mineral oil on the growth of rats depleted of vitamin A by a vitamin A depletion diet. A small curve of the control rats on the depletion diet is inserted for comparison. ⊕, xerophthalmia; †, death; ↓, day when cottonseed oil with vitamin A or mineral oil with vitamin A was begun.

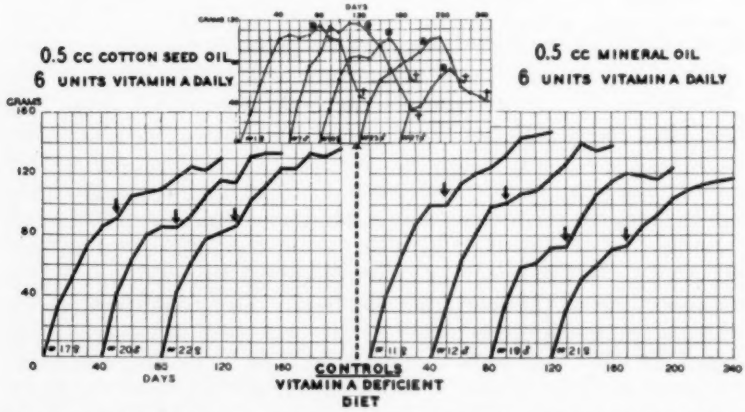

CHART 3.—The effect of 6 units of vitamin A. This was given daily in either 0.5 cc. of cottonseed oil or mineral oil on the growth of rats depleted of vitamin A by a vitamin A depletion diet. A small curve of the control rats on the depletion diet is inserted for comparison. ⊕, xerophthalmia; †, death; ↓, day when cottonseed oil with vitamin A or mineral oil with vitamin A was begun.

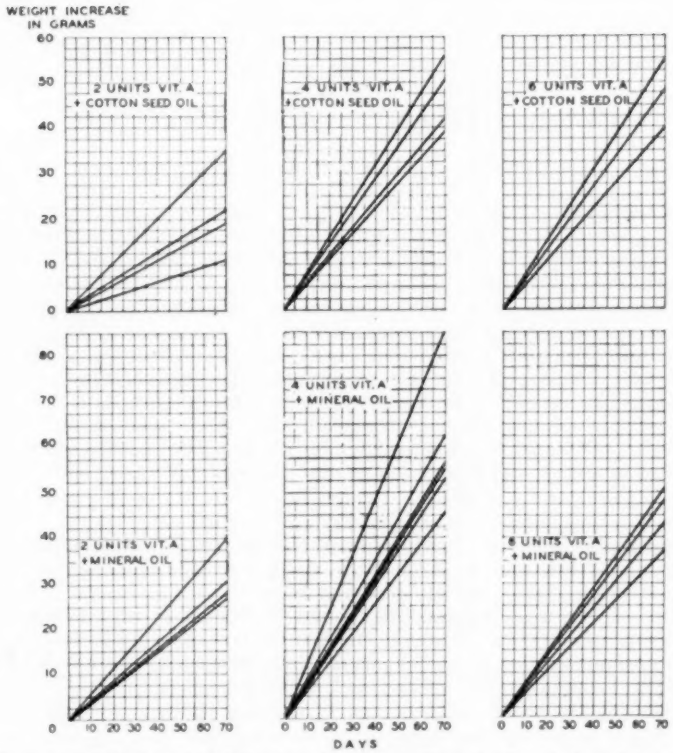
WEIGHT INCREASE IN GRAMS
2 UNITS VIT. A + COTTON SEED OIL
4 UNITS VIT. A + COTTON SEED OIL
6 UNITS VIT. A + COTTON SEED OIL
2 UNITS VIT. A + MINERAL OIL
4 UNITS VIT. A + MINERAL OIL
6 UNITS VIT. A + MINERAL OIL
DAYS

CHART 4.—Gain in weight following vitamin A. The relative gain in weight, during the 70 days which followed the depletion period when the animals received 2, 4 and 6 units of vitamin A dissolved in cottonseed oil compared to the gain in weight during the same period of the animals that received 2, 4 and 6 units of vitamin A dissolved in mineral oil.

Conclusions. 1. Three groups of rats, showing signs of vitamin A depletion, resumed as good growth on 2, 4, or 6 units of vitamin A in 0.5 cc. of mineral oil daily as rats receiving the same amount of vitamin A in 0.5 cc. of cottonseed oil daily.

2. Because of the preferential solubility of carotene in mineral oil, a sufficient amount of vitamin A should be taken with or dissolved in mineral oil whenever it is used as a cathartic or food substitute.

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BOOK REVIEWS AND NOTICES

THE ESSENTIALS OF MEDICAL TREATMENT. By DAVID MURRAY LYON, M.D., D.Sc., F.R.C.P. ED., Professor of Clinical Medicine, The University, Edinburgh. Pp. 448; 19 illustrations. Edinburgh: Oliver & Boyd, 1939. Price, 15/-.

THIS volume was written as a guide for undergraduate and practitioner, because of the "comparative neglect of this subject" in undergraduate instruction. The book is well written and contains much and very excellent therapeutic advice. Its chief defect, however, lies in its brevity. For, in the attempt to cover the whole range of medical treatment within the limits of this small volume, the author has at times given scarcely the barest essentials. Although the book might be useful to the student for review purposes, it would not serve as a reference volume for the practitioner.

R. K.

A HISTORY OF TROFICAL MEDICINE. Based on The Fitzpatrick Lectures delivered before the Royal College of Physicians of London 1937–38. (In two volumes.) By H. HAROLD SCOTT, C.M.G., M.D., F.R.C.P. LOND., D.P.H., D.T.M. and H. CAMB., F.R.S.E., Director, Bureau of Hygiene and Tropical Diseases; Member of the Colonial Advisory Medical Committee, etc. Pp. 1165; illustrated. Baltimore: The Williams & Wilkins Company, 1939. Price, $12.50 per set.

THIS valuable work, based on the Fitzpatrick Lectures for 1937–1938, deals chiefly with somewhat more than a dozen diseases (malaria, blackwater fever, yellow fever, trypanosomiasis, leprosy, cholera, plague, the avitaminoses, and so on) that are generally associated with tropical countries. The author, of course, recognizes that "Tropical Medicine" is not an accurate term: it necessarily includes diseases that occur also in non-tropical regions but are less common there, and others that were once erroneously thought to be restricted to tropical zones. It is also noted that some diseases (cholera, plague, leprosy), now mostly confined to torrid zones for reasons not connected with temperature, were formerly widespread in temperate regions. Other diseases have not yet spread beyond warm climates because their vectors have not yet flourished elsewhere.

Dr. Scott views the disease situation in warm countries when they first came under European rule, then traces the improvements effected. The state of the navy and mercantile marine and the army is considered, and here as elsewhere the British Empire furnishes the bulk of the material. In the 139 pages devoted to malaria, for instance, Laveran, Grassi, Celli, the Italians and the Jesuits receive credit, to be sure, but the picture is mainly built on the basis of British studies and activities.

Two "tropical" poisons are considered: the Akee poisoning first seen on the Gold Coast, and Jamaica Ginger Paralysis (Jake Paralysis) first recognized in 1930 in this country. The rôle of the Suez and Panama Canals and of the Slave Trade in the spread of disease is described in 3 interesting chapters devoted to these subjects.

A final chapter gives 15 brief biographies from Bontius to Ronald Ross, though such pioneers as Pringle, Lind, Cooke and Thomas Trotter receive due notice in the text.

Nine pages of bibliography and 65 pages of index testify to the careful and authoritative nature of this production. It has value both for the medical historian and the thorough student of tropical medicine, and especially in its portrayal of the British contributions to the subject.

E. K.

TREATMENT OF SOME COMMON DISEASES (Medical and Surgical). By Various Authors. Edited by T. ROWLAND HILL, M.D. (LOND.), M.R.C.P. (LOND.), Physician to the Southend General Hospital; Assistant Physician to the West End Hospital for Diseases of the Nervous System, etc. Pp. 398; 90 illustrations (several in color) and many Roentgen rays. Baltimore: The Williams & Wilkins Company, 1939. Price, $5.00.

NOT a textbook, but a series of practical monographs on treatment by 21 members of the staff of the Southend General Hospital, London. The subjects discussed are angina pectoris, heart failure, pleurisy, bronchopulmonary suppuration, anemia, cerebral vascular disease, digestive disorders of infancy and childhood, prophylactic treatment by immunization, malignant disease of the pharynx, obstructive jaundice due to malignant disease, hemorrhage from the intestinal tract, enlargement of the prostate gland, infections of the face and neck, suppurative lesions about the knee joint, head injury, uterine hemorrhage, delayed labor, shock during anesthesia, pre-anesthetic medication, Roentgen rays in the treatment of malignant disease, injuries to the skin and mucous membranes in radiation therapy, moles, warts and angiomata, ocular complications of certain disorders of the skin, earache, dental caries and postoperative wound complications. The presentations are concise, but adequate. It is the type of book that general practitioners seem to value highly. There is, however, too much material that belongs strictly in the province of specialists (*e. g.*, cholecystenterostomy, prostatectomy, drainage of the knee joint, deep Roentgen therapy of tumors).

R. K.

THE MALARIAL THERAPY OF GENERAL PARALYSIS AND OTHER CONDITIONS. By WILLIAM H. KUPPER, M.D., Formerly Resident Physician, Florida State Hospital and Special Physician Associated with the Station for Malarial Research, International Health Division of the Rockefeller Foundation, Tallahassee, Florida. Pp. 155 (lithoprinted); 8 illustrations. Ann Arbor: Edwards Brothers, Inc., 1939. Price, $2.25.

THIS concise monograph tells of the fever therapy movement, mechanism of cure in malarial therapy of general paralysis, different malarial parasites, cure of the induced fever, malarial therapy in syphilitic manifestations other than general paralysis, comparison of malaria with other non-specific agents, the influence of natural and induced malaria upon early syphilis, and malarial therapy in dementia precox and other non-specific conditions. It is believed that the reticulo-endothelial system, and not the fever, is the important factor; at first, the functions of this system are impaired, but following the fever they are improved. Malarial fever is preferable to that induced through electrical machines. The Anopheline mosquito is the insect of choice. The Rockefeller Institute affiliation has an efficient insectary designed by Dr. Mark F. Boyd. From 30 or more wild, caged mosquitoes, the ova are collected; these, having hatched in 2 or 3 days, if supplied with suitable nourishment will ripen in some 30 days and, from the developed larvæ, the mosquitoes emerge; since the insects have not been infected, they are without danger to the technician who permits daily blood feedings from his arms and legs; their subsequent inoculation is tedious work. The difficulties of rearing the mosquitoes having been overcome, this method is preferable for institutions to the commonly used methods of direct inocula-

tion with malarial blood. Statistics from a large hospital show that previously, the number of paretics discharged as improved was 2.6 per cent, and the death rate was 62.1 per cent; of a group treated with malaria, 33.5 per cent were discharged, and only 20.9 per cent died. Of the other diseases where malarial therapy has been tried, gonorrhea has been most responsive. The bibliography covers 25 pages. N. Y.

LIFE AND LETTERS OF DR. WILLIAM BEAUMONT. By JESSE S. MYER, A.B., M.D., Late Associate in Medicine in Washington University, St. Louis. With an Introduction by SIR WILLIAM OSLER, BT., M.D., F.R.S., Late Regius Professor of Medicine in Oxford University, England. Pp. 327; illustrated. St. Louis: The C. V. Mosby Company, 1939. Price, $5.00.

THIS work first appeared in 1912 with a characteristic Introduction by Sir William Osler. It is now reprinted with a "Present-Day Appreciation" by Dr. A. C. Ivy, Professor of Physiology and Pharmacy at Northwestern University. In the interim the importance of Beaumont's work has become more thoroughly appreciated—societies have been named for him, "shrines" created, and in 1929 it was his portrait that was chosen to adorn the medal of the International Congress of Physiology. Anyone interested in Beaumont can hardly dispense with this authoritative statement.

E. K.

LEE ON THE LEVEE (An Historical Novel). By RALPH CANNON. Pp. 188. New York: The Saravan House, 1940. Price, $2.50.

THIS pleasant novel about the young Robert E. Lee's engineering activities on the Mississippi has a special interest for medical readers in its protrayal of his friendship with the physiologist Beaumont, to whose experiments with St. Martin considerable space is here given.

E. K.

THE NEWER NUTRITION IN PEDIATRIC PRACTICE. By I. NEWTON KUGELMASS, B.S., M.A., M.D., PH.D., SC.D., Attending Pediatrician, Broad Street Hospital and Heckscher Institute, New York; Consulting Pediatrician, Lynn Memorial, Monmouth Memorial and Muhlenberg Hospitals, New Jersey, etc. Pp. 1155; 183 illustrations. Philadelphia: J. B. Lippincott Company, 1940. Price, $10.00.

THIS volume covers the entire field of nutrition in health and disease during infancy and childhood. The author's major premise is stated in the preface—"an understanding of the normal functions of the body in relation to each of the fifty essential nutrients (22 amino acids, 12 vitamins and 13 minerals) is the only basis for individualizing nutrition at all ages, types of constitution and levels of body functioning."

While there is a valuable collection of physiologic and nutritional data and innumerable useful diet lists, the Reviewer feels that the author does not follow this premise in the presentation of his material. It is highly questionable whether the fifty essential nutrients elements are all essential; certainly, the exact value and need for many of the fifty in human nutrition are still unproved.

Most of the approved nutritional procedures and régimes of the pediatric period are adequately presented, but many enthusiastic and unreserved recommendations of the author are by no means unanimously accepted. To cite just one of many—the careful study of Senn on the use of the author's hydrating solution in newborn infants is certainly not in agreement with the author's statements. M. R.

ELMER AND ROSE PHYSICAL DIAGNOSIS. Revised by HARRY WALKER, M.D., F.A.C.P., Associate Professor of Medicine, Medical College of Virginia, Richmond. Pp. 792; 295 illustrations. Eighth edition. St. Louis: The C. V. Mosby Company, 1940. Price, $8.75.

DR. WALKER, in revising Dr. Elmer's revision of Dr. Rose's work, has definitely improved on previous editions, not only by weeding out useless material and including new developments in the field, but by a better arrangement of the subject matter. The book is primarily intended for teaching physical diagnosis to students, and for this purpose it is adequate. Its chief virtue lies in its viewpoint that "physical diagnosis" refers to the whole patient and not simply the examination of the thorax and its contents. As a reference work, however, it is too abbreviated. Thus there is no mention of physical signs due to foreign bodies in the air passages, or those occurring in bacterial endocarditis of the right side of the heart. An interesting innovation is pale-green paper instead of white. R. K.

PRINCIPLES OF ORTHOPEDIC SURGERY. By JAMES WARREN SEVER, M.D., Assistant Professor of Orthopedic Surgery, Harvard Medical School; Orthopedic Surgeon, Children's Hospital, Boston; Associate Surgeon, Boston City Hospital, etc. Pp. 418; 221 illustrations. Third Edition. New York: The Macmillan Company, 1940. Price, $3.25.

A CONCISE, well-written book. Clearly printed; amply illustrated with clear cuts; good margins and nicely bound in fabrikoid.

This book should prove of value to medical students and those practitioners desiring a fairly comprehensive but not detailed text. It cannot compete with the larger definitive works of Whiteman, Campbell or Steindler. It can however be recommended as an authoritative work of considerable value. G. W.

CYCLOPROPANE ANESTHESIA. By BENJAMIN HOWARD ROBBINS, B.A., M.S., M.D., Associate Professor of Pharmacology, Vanderbilt University School of Medicine. Pp. 175; 40 illustrations. Baltimore: The Williams & Wilkins Company, 1940. Price, $3.00.

THIS excellent little volume is one more witness to the fact that anesthesia is assuming a place of its own in the medical world. It shows the need for coöperative endeavor on the part of the chemist, physicist, physiologist, pharmacologist and surgeon in the search for the "perfect anesthetic."

The book outlines the physical and chemical characteristics of cyclopropane. It discusses, on the basis of recent investigation, many undertaken by the author himself, the effect of cyclopropane on circulation, respiration, the gastro-intestinal tract, blood and other body tissues. Physiological principles are invoked and suggestions made for the application of these in the clinic. One wonders if the value of cyclopropane in obstetrics has been unduly praised and the dangers from explosion minimized. R. D.

SYNOPSIS OF OBSTETRICS. By JENNINGS C. LITZENBERG, M.D., F.A.C.S., Professor Emeritus of Obstetrics and Gynecology, University of Minnesota Medical School, Minneapolis. Pp. 394; 157 illustrations (5 in color). St. Louis: The C. V. Mosby Company, 1940. Price, $4.50.

THE author has brought the wisdom gained from long years of clinical experience into the preparation of this synopsis. Brevity marks the text, and practically every paragraph states an obstetric axiom. Emphasis is lent to many points by having the text printed in heavier type or italics. The volume consists of 38 chapters which deal with the normal course of

labor and the puerperium as well as the pathology, complications, and surgery of the subject. It is an excellent and a concisely written general review of obstetrics in a convenient form which should provide means for a quick review of the subject for either practitioner or student.

P. W.

DIABETES. Practical Suggestions for Doctor and Patient. By EDWARD L. BORTZ, A.B., M.D., F.A.C.P., Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Chief of Medical Service B, The Lankenau Hospital, Philadelphia, etc. With a Foreword by GEORGE MORRIS PIERSOL, B.S., M.D., F.A.C.P., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania. Pp. 296; 15 illustrations and 6 tables. Second Edition, revised and enlarged. Philadelphia: F. A. Davis Company, 1940. Price, $2.50.

THE present edition of this manual has been enlarged and revised particularly in the section dealing with insulin. The use of protamine zinc insulin and crystalline insulin, together with the differences in hypoglycemic, symptoms induced by both of these in contrast to those of standard insulin, is discussed. The illustrations are well chosen. An excellent table on the differential diagnosis of various types of coma is again included.

Separate chapters by collaborators are devoted to diabetes in childhood, diabetic surgery, dental care, care of the feet, and dietary management. The use of special diabetic food is condemned. The recipes for common dishes would be more valuable if the amounts of carbohydrate, protein and fat were given. The table of food values includes the amounts of vitamins, iron, calcium and phosphorus. Inclusion of U-10 insulin and of the U-10—U-20 syringe is of dubious value; likewise confusion may result from "calories per square foot" and metabolic "rate per square meter" in the same paragraph on page 63.

For patients and practicing physicians this manual is an excellent ready reference.

M. B.

A TEXTBOOK OF SURGERY. By JOHN HOMANS, M.D., Clinical Professor of Surgery. Compiled from lectures and other writings of 23 members of the Surgical Department of the Harvard Medical School. With a Special Bibliographical Index. Pp. 1272; 530 illustrations by WILLARD C. SHEPARD. Springfield, Ill.: Charles C Thomas, 1940. Price, $8.00.

THIS textbook, edited by Doctor Homans but compiled from the lectures and other writings of 23 members of the Surgical Department of the Harvard Medical School, has stood the test of time. First issued in 1931, it has been revised often enough and carefully enough to keep it well abreast of newer developments in physiology and surgery. While no textbook seems perfect, except perhaps to the author or authors, this one can be recommended without reservation as one which will fill the demands of the usual courses in surgery. The bibliographical index is particularly good, though text references to the bibliography might be of advantage. We shall hope for further revisions and additions to this valuable text as they are needed.

I. R.

SEX AND LIFE. FORTY YEARS OF BIOLOGICAL AND MEDICAL EXPERIMENTS. By EUGEN STEINACH, M.D., PH.D., Formerly Professor of Physiology at the University of Vienna. The scientific values adapted to the lay reader by JOSEF LOEBEL, M.D. Pp. 252; 67 illustrations (many in color). New York: The Viking Press, 1940. Price, $3.75.

THIS book first discusses the age-long ideas of the relation between Sex and Life before any scientific knowledge of the hormonal aspects of the

gonads had been developed. It then proceeds to a discussion of the relationship of the sex organs to the nervous system and of physical and psychic sex characters. Realizing that the generative organs control physical and psychic sex manifestations, the author transferred his attention to the transplantation of sex glands in animals—the field that is most widely connected with his name. He believes that through such transplantations sex characteristics could be maintained in a state of maturity. The effects of deprivation, castration, vasoligation or surgical reactivation, in animals as well as in the human, are discussed. The subject of senescence in both male and female is considered from a standpoint of his reactivation experiments. The comparative effects in veterinary medicine are appended. He describes in detail the entire operation of vasoligation, the operation to which his name has been attached.

The book closes with a rather conservative presentation of the effects of both the male and female sex hormones. It represents the first personal presentation, aside from a few case reports, of the long years of physiologic and biologic studies of the sex glands by one of the pioneers in this field. It is important in that in its presentation it is freed from any of the distortions or exaggerations usually connected with this man's experiments.

P. W.

THE PATHOLOGY OF INTERNAL DISEASES. By WILLIAM BOYD, M.D., LL.D., M.R.C.P., Ed., F.R.C.P., Lond., Dipl., Psych., F.R.S.C., Professor of Pathology and Bacteriology in the University of Toronto, Toronto; Formerly Professor of Pathology in the University of Manitoba, Winnipeg. Pp. 874; 353 illustrations and 4 colored plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, $10.00.

EARLIER editions have caused this book to be recognized as one of the most valuable and readable in pathology, from the standpoint of general physicians, pathologists and medical students. In the preparation of the third edition, a great deal of revision was not necessary; but a number of subjects have been brought up to date, such as the pathogenesis of lobar pneumonia and hemorrhagic pancreatic necrosis, and the etiology of glomerulonephritis. New material has been added on the relation of the pituitary to diabetes, vitamin K deficiency, internal coronary hemorrhage and other subjects. There are a number of good new illustrations. M. McC.

THE MANAGEMENT OF OBSTETRIC DIFFICULTIES. By PAUL TITUS, M.D., Obstetrician and Gynecologist to The St. Margaret Memorial Hospital, Pittsburgh, Consulting Obstetrician and Gynecologist to the Pittsburgh City Homes and Hospital, Mayview, etc. Pp. 968; 368 illustrations, and 5 color plates. Second Edition. St. Louis: The C. V. Mosby Company, 1940. Price, $10.00.

THE second edition of Titus' "Management of Obstetric Difficulties" has been revised to include some recent advances in various phases of the subject of obstetrics. Probably originally conceived as a book to meet the problems implied in its title, the volume really is a fine portrayal of practical clinical obstetrics. There are few situations which arise in obstetric practice for which a solution would be sought in vain in the text. Of particular note in the additions to this edition is a discussion of sulphanilamide in the infections of the reproductive cycle, although the author is conservative in the dosage suggested.

To obviate obstetric difficulties, he has given a thorough consideration of what Roentgen ray pelvimetry may signify in the diagnosis of disproportion.

Recent contributions on obstetric analgesia and anesthesia are well evaluated. There are many new illustrations which add much to the value of the book.

For the practicing obstetrician or the general practitioner without ready access to a consultant this book should continue to fulfill a definite need.

P. W.

AN INTRODUCTION TO GASTRO-ENTEROLOGY. Being the Third Edition of The Mechanics of the Digestive Tract. By WALTER C. ALVAREZ, Professor of Medicine, University of Minnesota, The Mayo Foundation, and a Senior Consultant in the Division of Medicine, The Mayo Clinic. Pp. 778; 186 illustrations. New York: Paul B. Hoeber, Inc., 1940. Price, $10.00.

THIS book, being an amplification of the author's well-known work on "The Mechanics of the Digestive Tract," will be welcomed by all gastro-enterologists. It brings up to date, including much new material, a connected story of the recorded data and opinions regarding the physiology of the digestive tract and at the same time presents Alvarez' application of such fundamental knowledge to clinical medicine. Whether or not one agrees entirely with his theory of an intestinal gradient of activity, one must admit that it seems to explain many puzzling phenomena.

As always Alvarez' discussions are to the point, informative and stimulating. Because the book presents reasonable explanations for many obscure clinical phenomena it should appeal to all practitioners of medicine, and because of the thoroughness with which it covers the literature and of its extensive bibliography it should be in the hands of all investigators in the field of gastro-enterology.

J. N.

FETAL AND NEONATAL DEATH. A Survey of the Incidence, Etiology, and Anatomic Manifestations of the Conditions Producing Death of the Fetus in Utero and the Infant in the Early Days of Life. By EDITH L. POTTER, M.D., PH.D., Instructor in the Department of Obstetrics and Gynecology, The University of Chicago; Pathologist at The Chicago Lying-in Hospital, and FRED L. ADAIR, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-in Hospital. Pp. 207; 31 illustrations. Chicago: The University of Chicago Press, 1940. Price, $1.50.

IN view of the increasing emphasis upon the conservation of human life, especially that of pregnant women and newborn infants, the present contribution is timely. In this small volume the authors have brought together pertinent facts regarding the following subject: 1, Birth rates, and those of stillbirths and infant deaths; 2, the characteristics of the normal fetus and infant; 3, a consideration of postmortem examinations; 4, a survey of the principal causes of fetal and infant death; 5, a chapter dealing with special pathology.

The authors note the declining birth rate in this country and the inadequacy of our statistics regarding the causes of stillbirth. Although they note a decline in the deaths occurring under one year of age, the deaths under one day of age have exhibited no significant change. Considerable space is devoted to the characteristics of the normal infant. This subject is important to the obstetrician as well as to the pathologist and the roentgenologist.

The volume as a whole was written for the purpose of showing some of the reasons for fetal and infant deaths and as a basis for further investigations. The authors, however, did not make any recommendations regarding the future, on the basis of their observations. The book will be a valuable asset to obstetricians, pathologists and others interested in infant death.

D. M.

NEW BOOKS

Diagnosis and Treatment of Head Injuries. By SIDNEY W. GROSS, M.D. F.A.C.S., Attending Neurosurgeon, Beth Israel Hospital; Associate Neurosurgeon, Morrisiania City Hospital; Adjunct Neurosurgeon, Mt. Sinai Hospial, etc., and WILLIAM EHRLICH, M.D., Associate Attending Neurosurgeon, Newark Beth Israel Hospital; Neurosurgeon, Barnett Memorial Hospital, Paterson, etc. Introduction by PERCIVAL BAILEY, M.D., PH.D., Professor of Neurology and Neurosurgery, University of Illinois, Chicago. Pp. 275; 94 illustrations. New York: Paul B. Hoeber, Inc., 1940. Price, $5.00.

Cyclopropane Anesthesia. By BENJAMIN HOWARD ROBBINS, B.A., M.S., M.D., Associate Professor of Pharmacology, Vanderbilt University School of Medicine. Pp. 175; 40 illustrations. Baltimore: The Willams & Wilkins Company, 1940. Price, $3.00. (Review, p. 111)

The Foot and Ankle. Their Injuries, Diseases, Deformities and Disabilities. By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor of Orthopaedic Surgery, Post-Graduate Medical School of Cook County Hospital, etc. Pp. 620; 303 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $9.00.

Convalescent Care. Proceedings of the Conference Held Under the Auspices of the Committee on Public Health Relations of The New York Academy of Medicine, November 9 and 10, 1939. Pp. 261. New York: The New York Academy of Medicine, 1940.

Obesity and Leanness. By HUGO R. RONY, M.D., Formerly Associate in Medicine and Chief of Endocrine Clinic, Northwestern University School of Medicine, Chicago; Formerly Attending Physician, Cook County Hospital, Chicago, etc. Pp. 300; 32 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $3.75.

Dynamics of Inflammation. An Inquiry into the Mechanism of Infectious Processes. (Experimental Biology Monographs.) By VALY MENKIN, Department of Pathology, Harvard University Medical School. Pp. 244; 50 illustrations. New York: The Macmillan Company, 1940. Price, $4.50.

El Corazón y La Circulación en Los Hipertiroideos. Consideraciones Sobre Fisiopatologia, Clinica y Terapéutics. By HÉCTOR GOTTA, Médico de la Primera Cátedra de Semiología y Clínica Propedéutica, Hospital Nacional de Clinicas. Pp. 104; 13 illustrations and 13 charts. Buenos Aires: "El Ateneo," 1938.

Pathological Histology. By ROBERTSON F. OGILVIE, M.D., F.R.C.P. (Edin.), Lecturer in Pathology, University of Edinburgh; Senior Pathologist, Royal Infirmary, Edinburgh; Pathologist, Deaconess Hospital, Edinburgh; Examiner in Pathology for the Triple Qualification. Foreword by A. MURRAY DRENNAN, M.D., F.R.C.P. (Edin.), Professor of Pathology, University of Edinburgh. Pp. 332; 220 photomicrographs in color by T. C. DODDS, F.R.P.S., F.I.B.P., Senior Technician, Pathology Department, University of Edinburgh. Baltimore: The Williams & Wilkins Company, 1940. Price, $8.50.

Cancer. A Manual for Practitioners. The Committee on Publication: GEORGE W. HOLMES, M.D., Chairman, ERNEST M. DALAND, M.D. SHIELDS WARREN, M.D., CHANNING C. SIMMONS, M.D., Editor. Pp. 284. Boston: Department of Health, 1940.

Chemistry and Medicine. Papers Presented at the Fiftieth Anniversary of the Founding of the Medical School of the University of Minnesota. Edited by MAURICE B. VISSCHER, Professor of Physiology at the University of Minnesota. Pp. 296; illustrated. Minneapolis: The University of Minnesota Press, 1940. Price, $4.50.

Manual of Peripheral Vascular Disorders. By DAVID W. KRAMER, M.D., F.A.C.P., Assistant Professor of Medicine, Jefferson Medical College; Assistant Physician and Chief Clinic Assistant, Vascular Clinic, Jefferson Hospital, etc. Pp. 448; 126 illustrations. Philadelphia: The Blakiston Company, 1940. Price, $6.00.

The Electrocardiogram in Congenital Cardiac Disease. A Study of 109 Cases, 106 with Autopsy. By MAURICE A. SCHNITKER, B.Sc., M.D., Formerly Resident Physician, Peter Bent Brigham Hospital and Assistant in Medicine, Harvard University Medical School, Boston, etc. Pp. 147; illustrated. Cambridge: Harvard University Press, 1940. Price, $3.00.

The March of Medicine. Edited by the Committee on Lecturers to the Laity of the New York Academy of Medicine, William C. White, Chairman. Pp. 168. New York: Columbia University Press, 1940. Price, $2.00.

NEW EDITIONS

Principles of Orthopedic Surgery. By JAMES WARREN SEVER, M.D., Assistant Professor of Orthopedic Surgery, Harvard Medical School; Orthopedic Surgeon, Children's Hospital, Boston; Associate Surgeon, Boston City Hospital, etc. Pp. 418; 221 illustrations. Third Edition. New York: The Macmillan Company, 1940. Price, $3.25. (Review, p. 111)

Clinical Parasitology. By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Colonel U. S. Army (Retired), D.S.M., Emeritus Professor of Tropical Medicine in the Tulane University of Louisiana, New Orleans, and ERNEST CARROLL FAUST, M.A., PH.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 772; 244 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, $8.50.

A Textbook of Pathology. By W. G. MACCALLUM, Professor of Pathology and Bacteriology, The Johns Hopkins University, Baltimore. Pp. 1302; 695 illustrations. Seventh Edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1940. Price, $10.00.

For years this has been one of the best and most successful textbooks of pathology. The reasons for its success are the clearly written and readable text and the excellent illustrations. The point of view is different from that of comparable books: pathologic conditions are arranged according to etiology rather than according to organs. The present edition introduces a number of minor changes; for example, conditions due to viruses are brought up to date.

The Compleat Pediatrician. Practical, Diagnostic, Therapeutic, and Preventive Pediatrics. For the Use of Medical Students, Internes, General Practitioners, and Pediatrists. By WILBURT C. DAVISON, M.A., D.Sc., M.D., Professor of Pediatrics, Duke University School of Medicine; Pediatrist, Duke Hospital, etc. Pp. 269. Third Edition. Durham, N. C.: Duke University Press, 1940. Price, $3.75.

Rewritten because of the many additions to pediatric knowledge of the past three years.

A Manual of the Common Contagious Diseases. By PHILIP MOEN STIMSON, A.B., M.D., Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Visiting Physician, Willard Parker Hospital, etc. Pp. 463; 54 illustrations and 6 plates, 4 in color. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, $4.00.

Treatment by Manipulation. By A. G. TIMBRELL FISHER, M.C., M.B., CH.B., F.R.S.C. (Eng.), Co-Trustee and Member of Executive and Research Advisory Committees of Empire Rheumatism Council; Corresponding Member of the American Academy of Orthopædic Surgeons, etc. Pp. 255; 68 illustrations. Third Edition of "Manipulative Surgery." New York: Paul B. Hoeber, Inc., 1939. Price, $3.75.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

ANEMIA IN PREGNANCY.

INCREASING interest in recent years in the classification of the anemias in general has led to a more careful study of the blood in pregnant women. No attempt will be made here to review the subject historically. Reviews of the older literature are available in the reports of Pepper,[55] Bland, Goldstein and First,[13a,b] and in the more recent report of Evans.[24] Pepper aptly points out that much of the literature antedates the era of modern hematology and this, together with the incompleteness of case reports, makes interpretation of earlier work difficult and at times impossible. The reports only of the last several years will be detailed here, together with pertinent information of interest from earlier sources.

The pregnant woman undergoes many physiologic changes which affect profoundly the functions and reactions of the entire organism. Such changes in the blood would necessitate the establishment of physiologic standards for pregnancy if any differences from the non-pregnant state developed. Thus Bethell and his associates[11] have defined true anemia of pregnancy as a condition characterized by decrease in the red blood cells, hemoglobin, or both, below levels considered as physiologic for gestation. These standards and the physiologic changes necessitating their establishment will be discussed below.

There are a number of ways in which anemias in pregnancy have been classified. Osler,[53] in 1919, divided them into four groups, severe anemias, those due either to postpartum hemorrhage or sepsis, and postpartum anemia. Alder,[3] in 1924, grouped them either into anemias *with* pregnancy, such as chlorosis, congenital hemolytic jaundice, posthemorrhagic anemia, and others, or anemias *from* pregnancy including "physiologic anemia" and the pernicious anemia of pregnancy. Evans[24] classifies them as: 1, deficiency anemias, either microcytic or macrocytic, as will become evident below; 2, as anemia of hemorrhage; 3, anemia of sepsis; 4, hemolytic anemia; and 5, anemia with pregnancy as a complicating factor. Smallwood[61] has published a similar classification. Other classifications incorporating red cell morphology are in use. The present discussion will be grouped under three general head-

ings: 1, the physiologic changes in the blood in pregnancy; 2, anemias produced by pregnancy; and 3, the anemias incidental to pregnancy, or rather the occurrence of pregnancy in anemic women.

The Physiologic Changes in the Blood in Pregnancy. These changes will be considered only from the standpoint of red blood cells and hemoglobin. For many years confusion reigned as to the presence or absence of a "physiologic anemia" of pregnancy. Not only was such a possibility both confirmed and denied but actual increases in the number of red blood cells were also reported. As far back as 1881 patients have been described as having an increase in plasma and the necessity of differentiating this dilution of cells, or hydremia, from true anemia was pointed out. Since then many observers[24] have worked on this problem and careful studies of the blood in normal pregnant women have shown reduction of red blood cells and hemoglobin values for most patients. Kühnel,[38] in 15 women, found reductions in the number of red blood cells as early as the eighth week, and progression until the sixteenth to twenty-second week, with a rise then at about the thirty-fourth week due to diuresis at that time. Hydremia is a likely explanation of the early changes and reliable methods[21] applied to the woman at intervals throughout pregnancy have shown increases in blood and plasma volume beginning in the first trimester and reaching by the thirteenth week 16 and 18% respectively. At term these figures are 23 and 25%. Hemoglobin and total cell volume increase but do not keep pace with the blood and plasma volume and the hemoglobin and red blood cell determinations per unit volume of blood are diminished. Others in recent years have definitely shown this physiologic change as well.[57] The change progresses until about the twenty-sixth week. Thomson and associates[68] found increases in plasma volume up until the ninth month. Oberst and Plass[50] and Feldman and his associates[26] reached similar conclusions. Strauss and Castle,[66b] in their examinations of the blood of 200 women in different months of pregnancy, and in a smaller group followed from month to month throughout pregnancy, found in general a steady decline in the erythrocyte count, with lowest counts usually at the end of the second trimester. These changes did not correlate with age or parity. A rapid gain of approximately 500,000 red blood cells per c.mm. took place within a week after parturition. Similar observations of a sudden postpartum increase of red blood cell count have been repeatedly reported.[28] The rapidity of the gain, it has been pointed out,[66b] is evidence that blood formation is not entirely responsible. Using the results of Keith, Rowntree and Geraghty,[36] that the average blood volume of women decreased 1100 cc. within 7 to 10 days postpartum, while blood loss was only about 300 cc., they calculated that the changes in red blood cell count postpartum, as determined by them, could be accounted for by change in blood volume, and conversely the decrease in red blood cell concentration observed in the first 6 months of pregnancy could be explained on the basis of increasing blood volume.

All do not agree that hydremia may account for all the changes seen. Some feel that actual anemia based on inadequate diet and gastrointestinal disturbances may possibly play a part, as may infection, which often causes anemia, already established, to become worse in

pregnancy.[44] Two theories of the older literature, which have very little supporting evidence, are that of hemolysis and toxic hemolysins from the fetus or placenta[4,34] and toxic inhibition of the bone marrow. None of these toxic factors has been proven to be factual.[66b] It is interesting to note that the fall in hemoglobin may be checked by the administration of iron[11,71] even when the hemoglobin rises quickly after delivery. Such evidence has so far apparently not been explained on the basis of hydremia.

In the face of the evidence on hand one cannot deny that the fall in hemoglobin and red blood cells in pregnancy is at least partially due to dilution which is fully established by approximately the twenty-sixth week and does not indicate anemia. There is a reluctance,[24] and rightfully so, to calling this change anemia, because, since there is evidence that hemoglobin and red blood cells increase though not as rapidly as the plasma, there are likely more hemoglobin and red blood cells functioning in the blood stream than in the non-pregnant state. Caution must be used in the interpretation of such findings. Simple hydremia would be expected merely to dilute the cells which are normal in size and hemoglobin content.[27]

The problem of differentiation of these changes from true anemias occurring as clinical entities in pregnancy becomes evident. The question immediately arises as to how extensive these changes may be and what level of hemoglobin we may use below which we can disregard the possibility of hydremia in diagnosis and assume true anemia to be present. In other words, we must establish a level for hemoglobin and red blood cells considered physiologic for pregnancy and judge the presence of anemia upon those standards. As will become evident from remarks under *Microcytic Anemia*, below, careful selection of normal patients is necessary. Such a level is not definitely established. Dieckmann and Wegner[21] consider the level to be 10 gm. hemoglobin per 100 cc. blood. Watson[70] places it at a lower figure, 7.7 gm. hemoglobin (55% Sahli), and states that any patient with a hemoglobin level of 60% or less should be investigated and anemia ruled out. Bethell and his associates[11] set the figures at 10 gm. hemoglobin and 3,500,000 red blood cells.

Anemias Produced by Pregnancy. It is evident that in certain instances true anemia may be present with values close to or exceeding the above levels. Hence it is important that the blood of the pregnant woman be checked. Anemia is often not recognized, if mild and without symptoms, at a very time when it is simplest to treat. If unrecognized, it may possibly play a rôle in the development of complications of pregnancy. It is probably one of the most frequently overlooked complications itself and yet there are generally satisfactory means to combat it.[44]

Pregnancy may act in some way to produce anemias which have their counterpart outside pregnancy. Hemorrhage, infection, inadequate use of necessary dietary principles for proper hematopoiesis are a few examples of such conditions. Concerning the character and treatment of anemias resting upon such bases as infection and hemorrhage nothing more will be said here. The removal of the etiologic agent, general measures, the use of chemotherapy, and adequate iron

supplies, where indicated, are the same as in similar instances outside the pregnancy state.

Microcytic Hypochromic Anemia. The frequency of anemia in pregnancy points definitely to factors as causes which have a direct relationship to the gravid state. It is known that pregnancy exerts an increased demand upon the mother for dietary requisites and it is particularly true that unless these women are directed in dietary choice they may not increase their intake of food to meet the new requirements. Furthermore, the diet may have been borderline or inadequate before the onset of pregnancy. They may feel no apparent need for an increase in certain dietary factors and continue to ingest the diet previously taken, whether or not it is adequate for their old or new physiologic state. Vomiting of pregnancy, gastro-intestinal disturbances, and peculiar dietary desires may also account for the deficiency. Likewise, the pregnant woman may develop certain physiologic changes which make for a more difficult utilization of erythropoietic materials.

It is true that anemia is not uncommon in general in women of childbearing age, particularly in certain parts of the world. For example, in a study in Scotland,[18] anemia was found in 16% of adolescent women and 45% of adult women. These patients supposedly represented a cross-section of the poorest classes of the population of Aberdeen and nearby areas. They did not present themselves for medical examination because of symptoms of ill-health. Other figures[46] tend to confirm these findings in the British Isles but not consistently in the United States,[45,52] and suggest the importance of the economic status.

In pregnancy, anemia is very frequent, particularly the hypochromic variety.[13a,29,30,43,56] Reid and Mackintosh,[56] in another British report, determined the hemoglobin level in 1108 pregnant women and 10.2% gave a reading below 70% (Haldane). The anemia was always hypochromic and division of the women on the basis of income showed a higher incidence in the lower income group. Parity had little influence on the degree of anemia, and age, work outside the home, or abnormality in pregnancy had no recognizable influence. In Cape Town,[43] similar results have been found. The hemoglobin values were lower in multiparæ and were higher in Europeans with higher incomes, and higher than in the colored race, nearly all of whom had lower incomes. References on economic status by other authors are quoted.

In this country, Bland, Goldstein and First[13a] found definite anemia, with red blood cell counts below 3,500,000 in one-half of 200 ward patients, while only about one-fourth (26%) of 100 private patients showed the same reduction. Hemoglobin values below 74% occurred in 82 and 62% of the patients, respectively. No relationship to parity, age, or blood pressure was evident and such possible etiologic factors as ill-health, foci of infection, toxemia, and syphilis were investigated but the extent of their influence was not sufficient to be determined. It was noted that in 34 of 48 women (71%) with red blood cell counts below 3,500,000 in the last trimester, rapid recovery took place postpartum. While hydremia played a part in these instances, and while anemia occurred in both groups, the distinct differences in the two economic groups is apparent. In another study these same authors[13b]

found in 1000 patients examined at various periods of gestation that 47.4% gave evidence of distinct reduction in red blood cells below 3,500,000 and 58.6% reductions in hemoglobin values to 70% (Dare) or less.

Greene[30] studied 229 white and 267 colored pregnant women. Hemoglobin values averaged 67 and 62.6%, respectively. About 75% of the white and 85% of the colored women had hypochromic anemia in the last 2 months of pregnancy. The anemias were reactive to iron. The differences in the two economic groups were again evident, although both groups had a high incidence of anemia. In another study[15] of 404 negro women, dietary deficiencies were found but were not considered wholly responsible for the anemia present. Labate[39a] found anemia in 48% of 881 patients in labor, 71% of whom had received no iron during the prenatal period. He believes that adequate diet is not enough to prevent anemia in pregnancy. Watson[70] found in 500 pregnant women hemoglobin values between 55 and 75% (Sahli) in 81%.

Despite the fact that all these series have not used comparable hemoglobin levels for estimation of anemia and have not considered the physiologic standards of the gestation period, many have, but if one definitely considers such levels the incidence of anemia is still high, as can be seen from some of the statistics given. Adair *et al.*[2] found 63.2% of pregnant women apparently anemic on non-pregnant standards and only 11.6% on standards of 10 gm. hemoglobin and 3,360,000 red blood cells. These results are low compared to those above and to those of Bethell,[10] who found 70% of 66 pregnant subjects with blood values too low to be accounted for on hydremia alone.

The influences of economic status are evident in all reports in which comparison of such groups has been made. It is significant that in 45 patients reported by Davies and Shelley[19] without anemia in pregnancy, 42 had a satisfactory dietary history. Dietary influences are bound up closely with economic conditions. Bethell *et al.*,[11] in finding true anemia in 54% of 158 clinic patients, state that it results most often from deficiency or impaired utilization of iron and also inadequate protein intake, the latter not responding to iron therapy alone. This group will be discussed further under *Macrocytic Anemia*. Strauss and Castle[66b] found that the type of dietary deficiency, such as low-protein and iron intake, was the same as that noted in other patients with hypochromic microcytic anemia.

That anemia occurs in all groups regardless of economic status indicates other possible factors. One of these appears to be the function of the gastro-intestinal tract. It is significant that in the observations of Strauss and Castle[66b] no appreciable anemia occurred in patients with a normal intake of food and also a normal gastric acidity. That hypochromic microcytic anemia may occur in non-pregnant women taking an amount of iron usually considered adequate, when there is a reduction in or absence of free hydrochloric acid in the stomach, is well known, has been emphasized many times and need not be repeated here. This factor appears at times to be important in pregnancy. It has been shown, for example,[66b] that when patients take comparable diets the hemoglobin loss in pregnancy varies with the gastric acidity.

Likewise, gastric analyses on 24 women in one study[66a] showed that 75% of the patients did not secrete normal amounts of free hydrochloric acid or pepsin during more than one-half the period of pregnancy. Another study,[39b] however, does not give such nicely correlated results. In 56 women, 52 of whom were in the last trimester, normal acidity was found in 42 (75%), hypochlorhydria in 9 (16%) and achlorhydria in 5 (9%). Labate does not believe a precise correlation is to be made between hypoacidity and anemia but that it may accentuate anemia from other factors. Davies and Shelley[19] found gastric secretion was usually normal when anemia was absent in pregnancy and that reductions in acidity were temporary. Of some interest is a study[14] on gastrectomized dogs. In 5 dogs in 15 pregnancies, marked to severe anemia occurred 11 times. Only once did anemia develop in 12 normal dogs in 12 pregnancies.

Also important in the production of anemia appears to be the fact that despite any deficiency in hematopoietic materials, the fetus continues to exert demands at the expense of the mother.[66c] It is rare that the infant is born anemic. In those rare instances where anemia of the newborn does occur, the mother is not necessarily anemic.[31] Even with anemic mothers, the red blood cell counts and hemoglobin of the infants are normal for that period of life.[66c] In fact, maternal anemia has been reported as associated with greater fetal polycythemia,[29] although such infants may develop anemia in the first year. The demand on the mother by the fetus for essentials of hematopoiesis has been likened to a chronic blood loss from other causes and represents a drain on the mother, especially in the latter part of pregnancy. The iron stores for the fetus must come either from the iron stores of the mother or from her food.[32] There are said to be 500 mg. of iron in the average fetus. Heath and Patek[32] state that if 10% reduction in hemoglobin results from hydremia which may account for hemoglobin levels to about 70%, a further reduction of 20% due to demands of the fetus for iron would reduce the hemoglobin to 50%, assuming no stores nor food source in the mother. With inadequate intake of iron, one may see that reduction of hemoglobin from fetal demands is likely and that repeated pregnancies, especially if frequent, might produce iron deficiency and anemia. Others, however, do not emphasize the fetal demands. The total additional requirement of iron incident to pregnancy has sometimes been given at lower figures than those stated above, about 250 mg.,[11] an amount in 500 cc. of blood. Nevertheless, infants from anemic mothers during the first year may develop moderate to severe anemia which may be prevented by administering iron to the mother during pregnancy, or corrected by a like procedure on the infant.[46] Such anemias appear to result from deficient storage of iron by the fetus because of a deficient maternal supply. Experiments on rats[6] bear out this contention.

Strauss and Castle[66b] found that anemia in pregnant women differed in no distinctive way from that outside pregnancy. Whether or not dietary deficiency results from inadequate intake or increased demands, it eventuates in the same pictures. To quote, "In short, then, in pregnancy the combination of the loss of blood building materials to the body, the lowering of the gastric acidity, and, in many cases, the

alteration of the diet of the patient, produces anemia by the same mechanisms that produce similar types of anemia in the non-pregnant individual."

The therapeutic requirements are clear so that the use of an adequate diet, iron, dilute hydrochloric acid, and other procedures, as in idiopathic microcytic anemia, is indicated.

Macrocytic Anemia of Pregnancy. True Addisonian pernicious anemia appears to be rare in pregnancy. However, the association of pernicious anemia with pregnancy had early beginnings. Many of Biermer's cases were in pregnant women.[55] In the earlier literature, lively discussion took place as to the rôle of pregnancy in pernicious anemia. At that time, however, diagnostic criteria were not as rigid as at present and the validity of many older reports must be looked upon with great suspicion. Any grave and severe anemia may have been called pernicious.

Macrocytic hyperchromic anemia of the pernicious type occurs with varying frequency in pregnant women.[9] Evans,[25] in England, did not find one instance of severe anemia in records of over 4000 pregnancies in the years, 1926–27. Richter, Meyer, and Bennett,[57] in this country, found no case in a year's survey of a service averaging 400 to 500 deliveries per month. However, Stevenson,[64] in Glasgow, found 30 patients in 6 years and Abramson,[1] in Sweden, 9 patients from 1933 to 1937. The incidence in relationship to deliveries is not stated. In general, frequency in temperate climates is said to be 1 in 10,000. Mays[47] found 4 in 9000 deliveries in Louisiana. In a report in 1939, Ritter and Crocker[58] state that only 1 case induced by pregnancy has been observed on the maternity service of the Philadelphia General Hospital. Strauss and Castle,[66c] in a study of 36 severe anemias of pregnancy, found 30 of the microcytic and 6 of the macrocytic type. The high incidence in India will be discussed below.

Clinically, the anemia tends to develop in the third trimester. Onset may be sudden or gradual. It may be discovered in the puerperium when starting in the last month of pregnancy and it has been called puerperal anemia by some.[8] Color indices are above 1, platelets and leukocytes are normal or diminished in numbers, mean corpuscular volume is increased, the blood picture in general simulating that seen in typical Addisonian pernicious anemia.[66c] Unlike true pernicious anemia, there is no relapse with omission of specific therapy following delivery, and achylia gastrica is not uniformly present. The gastric acidity varies. It may be normal, reduced, or free hydrochloric acid may be absent following histamine stimulation. In 2 of Strauss and Castle's 6 patients[66c] achylia was present. Two years later 1 of these women had normal gastric acidity and a subsequent pregnancy was not accompanied by macrocytic anemia, although hypoacidity occurred. Differential diagnosis includes the same diseases as pernicious anemia outside of pregnancy and includes thyroid disease, toxemia of pregnancy, endocarditis, sepsis, and other simulating conditions.[67]

The anemia has been attributed to various causes, especially in the older literature. These are reviewed by Studdiford.[67] The efficacy of brewers' yeast, particularly in reports from India, suggests an absence from the diet of the extrinsic factor of Castle. Castle's own observa-

tions suggest that it may be due to a deficiency state resulting either from a lack of extrinsic factor in the diet or from a lack of intrinsic factor in the gastric juice. Others have supported the latter view in certain instances.[51] The lack of intrinsic factor appears to be a temporary one, with return following delivery.

Liver preparations would be efficacious in the treatment in either instance and with adequate treatment by this means the old mortality rates of 40 to 70%[4] have been reduced until, with early recognition and treatment, almost all should recover. Transfusion is important in those seriously ill until response to liver therapy occurs. Termination of the pregnancy is not necessary. At times factors producing hypochromic anemia may also be present and then iron preparations are also indicated.

Bethell's group[11] has found in the mild anemias of many pregnant women a blood picture of reduced red cells with slightly elevated mean corpuscular volumes and color indices. This they ascribe to a nutritional basis, probably a lack of adequate dietary protein and suggest that when it is more severe it is probably the pernicious anemia of pregnancy. Elsom and Sample[23] also have investigated macrocytic anemia in pregnancy resembling pernicious anemia, and, like Bethell, have related it to dietary factors. The temporary nature of the disease, as stated above, suggests some type of temporary deficiency. The report of Strauss and Castle referred to above describes patients on poor diets late in pregnancy but did not indicate any possible single specific deficiency other than general statements concerning extrinsic factor. Elsom and Sample put 8 pregnant women on diets supplemented for adequacy in everything but vitamin B complex. Macrocytosis, increased mean cell volume and hemoglobin, reticulocytosis, along with other changes seen in pernicious anemia, sprue, and tropical macrocytic anemia occurred. Gastric acidity was not changed. The changes were greatest at the time the diet became theoretically inadequate in vitamin B. Administration of brewers' yeast or liver extract relieved all the characteristic changes and there was no significant difference in the effectiveness of these 2 therapeutic agents.

While Elsom tried to relate these changes to vitamin B, Bethell tried to relate similar changes to protein intake. Both reports indicate an anemia which could be the forerunner of a more severe macrocytic anemia as seen in pregnancy and emphasize the possibility of an extrinsic cause of a pernicious anemia of pregnancy as well as the possible temporary derangement in production of intrinsic factor.

There is little information concerning any relationship between macrocytic anemia of pregnancy and the blood picture of the newborn.[58] Without treatment of the mother, the infant's blood picture may be normal. The normal fetal blood picture, interestingly enough, resembles that of pernicious anemia subjected to effective continuous and potent stimulus to blood formation.[72] Ritter and Crocker[58] report anemia of the newborn in an infant born of a mother with macrocytic anemia. They believe that the anemia of both the mother and infant was due to dietary deficiency.

Particular mention must be made of the macrocytic anemia of pregnancy in India. Its incidence there is approximately 300 times the

European and American estimates, and good therapeutic results have been reported by Wills and others in the use of brewers' yeast, again leading to the possibility, as in Elsom's, Bethell's, and Strauss and Castle's reports, of dietary factors in the etiology of the clinical picture. For the work of Wills and others on tropical macrocytic anemia, and the relationship of brewers' yeast, liver, and other therapeutic agents to this type of anemia, the reader is referred to recent Indian reports.[16a,17,49]

The amazing number of cases in India has led to considerable study of the patients in that country. Most interesting is the recent report of Chatterjee[16a,b] who has reviewed some of the striking findings in these patients. It is apparently one of the commonest anemia syndromes in India, occurs seasonally with highest incidence in September, and affects all religions and races. Early in pregnancy it starts as a mild normocytic anemia (which may be hydremia) and passes through the microcytic to a severe macrocytic stage. It is observed only in pregnant women. There is free hydrochloric acid in the stomach, and bilirubin of the blood, icterus index, and red blood cell fragility are normal. The Van den Bergh reaction is negative and urobilinogen is absent from the urine, factors against an hemolytic origin. Reversal of the albumin globulin ratio of the blood has been observed and anasarca is common. Blood cholesterol falls markedly. Iron therapy is of value in the first and second stages with normocytic or microcytic cells. A third stage with microcytic or normocytic but hyperchromic cells reacts to liver therapy. In the fourth stage, with hyperchromic macrocytic anemia, transfusion alone is of help, but cholesterol therapy may be of some benefit.

The concept one gains from the stages and development of this anemia brings to mind the possibility of a clinical entity distinct and different from the pregnancy anemias seen in the Americas and Europe. However, the stages through which the patients pass resemble closely the effects of hydremia and the microcytic hypochromic anemia usually seen in pregnancy changing later into a macrocytic anemia, as seen in this country, but the lack of response to liver, reported in the fourth stage, is unexplained upon such a basis. The Reviewer, having never seen such patients, feels incompetent to interpret the findings.

Hemolytic Anemia. There is little evidence to support the possibility of an hemolytic factor, coming from the placenta or elsewhere, and responsible for hemolytic anemia in pregnancy. In the older literature Hofbauer[34] postulated an hemolysin produced in the chorion as the cause of maternal blood destruction in early pregnancy, a theory favored by the increased iron content of the urine of pregnant women. The theory was advanced to explain the "physiologic anemia."

Pregnancy may occur during the course of certain hemolytic anemias, which will be considered below. However, there are those[24] who believe that certain cases reported from time to time may be hemolytic and have the characteristics of Lederer's anemia. Lederer's anemia has been reported in the puerperium.[22] This type of anemia responds dramatically to blood transfusion, a procedure of temporary benefit only in the other types of anemia seen in pregnancy. In several reported cases[35,40a] there has been such a response to transfusion. Such evidence is, however, quite unsatisfactory in classifying these

patients and if the diagnoses were established there would still remain the problem of determining whether such anemias are incidental to or definitely related to pregnancy.

Anemias Incidental to Pregnancy. The possibility exists of pregnancy occurring in women with any type of anemia seen in the childbearing age; for example, anemia of blood loss, acute or chronic, infection, nephritis, leukemia, syphilis, true Addisonian pernicious anemia, and others. Hence, we may find, associated with pregnancy, any type of anemia occurring in the childbearing age outside of pregnancy and it may develop before or during the course of the pregnancy. There are, however, certain factors which tend to prevent the occurrence of pregnancy in anemic women. Anemia, of and by itself, is a commonly known cause of sterility and abortion.[20,48,69] Meaker states that "Anemia has a striking effect; even the milder grades produce considerable depressions of spermatogenesis and presumably of oögenesis." There is, as well, at least one anemia which appears to have an added effect in producing sterility, namely sickle-cell anemia.

Sickle-cell Anemia. This condition, confined almost exclusively to the colored race, represents most likely a congenital defect in red blood cell formation associated with considerable numbers of sickle-shaped red blood cells, and characterized clinically by anemia, bouts of abdominal pain with gastro-intestinal symptoms, cardiac changes, and leg ulcers. In the active phases of the disease pregnancy is a rarity. In 1934, Lash[41] found only 2 cases in the literature and reported another. Richter, Meyer and Bennett[57] observed a patient with sickle-cell anemia who delivered a live term baby. In 1936, Killingsworth and Wallace,[37] in a general study of sicklemia (sickle-cell trait), mentioned a patient with active sickle-cell anemia in the fourth month of pregnancy. In the same year Sharp and Schleicher[60] reported a patient with active disease followed through pregnancy. In 1937, 2 additional reports appeared, 1 by Lewis[42] and 1 by Sodeman and Burch.[63] Both stress the possibility that pregnancy may activate the latent disease. Page and Silton[54] just recently reported 2 cases of sickle-cell anemia and again discuss the possibility of exacerbation of the disease by pregnancy. Lewis stressed the disease as a possible cause of abortions. Sodeman and Burch emphasized also the effects on fertility. In only 4 reported patients has a live full-term baby resulted.

The exact mechanism by which active sickle-cell anemia may cause sterility is not clear. Anemia itself is a cause of sterility and abortion, as mentioned above. Because of the unsatisfactory methods of treatment of sickle-cell anemia the presence of anemia for long periods of time, even through the adolescent period into adult life, may have a profound effect upon the reproductive functions. Then, too, the disease itself, aside from the mere presence of anemia, may affect in some unknown manner the reproductive function.

Splenic Anemia. Those anemias associated with splenomegaly which are generally included under the vague term "splenic anemia" are sometimes complicated by pregnancy. The reported cases have been reviewed by Serbin.[59] Allen's report[5] of 2 cases in 1924 recorded sudden death during delivery in 1 patient and survival of the second. The latter patient was treated by Roentgen radiation and in a second

pregnancy therapeutic abortion was done followed by sterilization and later by splenectomy. There was no liver involvement. Other similar patients have been reported,[7,12,33,40b,59 1][62] with spontaneous rupture of the spleen at the third month, splenectomy performed, and term delivery. Progression of the anemia has occurred. Splenectomy during gestation, as in the case cited above, has been done in other patients[33] with term delivery. In some instances[7,40b] splenectomy has been done following termination of the pregnancy.

In general, pregnancy has aggravated the syndrome, although the reverse does not seem to be true.[59] Serbin emphasizes the use of both medical and surgical measures if the pregnancy is to terminate successfully with improvement of the patient's state. Preliminary medical therapy, with transfusion followed by splenectomy, seems indicated. Transfusion and splenectomy are important procedures, but when the condition is severely aggravated by pregnancy, even radical treatment may fail. Roentgen ray over the spleen, especially its intensive use, is not recommended during pregnancy.

As far as diagnostic aid is concerned, the statement is made that in normal pregnancy the spleen does not undergo any appreciable hypertrophy; enlargement during pregnancy is usually due to preëxisting disease.[59] A moderately enlarged spleen, up to 800 gm., may not disturb pregnancy. Up to 1000 gm. or more, some embarrassment is likely to occur because of encroachment on the space required by the growing uterus.

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PEDIATRICS

UNDER THE CHARGE OF
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HEART DISEASE IN CHILDREN.

In the last two decades a striking advance in the cardiology of adults has taken place in the knowledge of the involvement of the coronary arteries and the resulting changes in the myocardium to the extent that the subject as taught 20 years or more ago has come to be inadequate in considering heart disease in adults today. While no such radical changes have occurred in cardiology of childhood, still there are many contributions to be found in the current literature, and some of these tend to alter the concepts of the pathology, treatment and prognosis of these conditions. It is timely to analyze these contributions and evaluate the changes which we should make in our study and treatment of these conditions.

Heart disease in childhood should be divided into two main headings,

congenital and acquired. The congenital lesions are mainly developmental although some occur as the result of disease in the mother. Dry[9] reminded us that the developing mammalian heart assumes functional activity at a very early stage of gestation. A study of the embryology and comparative anatomy of the heart is essential to an understanding of the cause and mechanism of human congenital cardiac anomalies. From the simple tube-like structures septal formations divide the auricle, the ventricle, the bulbus cordis and the common aorta or truncus arteriosus each into two sections. Next there is torsion of the cardiac tube followed by development of the bulbus cordis, incorporation of the sinus venosus into the right auricle, the evolution of the aortic arches, some becoming obliterated, while others become the permanent arch, pulmonary vessels and their branches. Finally there is closure of fetal channels after birth. Associated with each of these processes anomalous developments may occur and congenital cardiac lesions may be classified accordingly. The author's classification of congenital lesions does not differ materially from Maude Abbott's and others found in textbooks on the subject.

Along somewhat similar lines Bredt[5] attempted to evaluate the embryogenesis of certain maldevelopments in the light of their morphology and of current, but often controversial, theories. In his presentation of hearts with two or more anomalies, he has considered whether such multiple malformations were a necessary result of some primary failure of development in the sense that a septal defect may be secondary to, or compensatory to, stenosis of an ostium, or whether the multiple maldevelopments may be brought about by a factor acting independently on different parts of the developing organ. In another section he dealt with atresias and stenoses of the cardiac cavities and the ostia. In the discussion of persistent truncus arteriosus communis, he expressed the belief that when the trunk had a valve of three rather than four segments the anomaly was the result of suppression of the pulmonary artery or aorta and not simple persistence of an originally single truncus arteriosus. In another section he described some unusual auricular defects, such as an unusual defect of the septum, congenital bands of the interior of the auricles and atresia of the mouth of the coronary sinus. In the final section he presented failures of development of the coronary arterial system.

In discussing the progress in the recognition of congenital heart disease, McGinn and White[26] stated that in 7500 postmortem examinations performed at the Massachusetts General Hospital in the last 40 years, congenital heart disease was found 67 times (an incidence of 0.9%). Of the 67 patients with congenital heart disease, 21 were under 1 year of age. Of the 7500 autopsies, 3400 were made in the last 15 years, and in this group the incidence of congenital heart disease was 1.2%. The most common congenital defect in the latter group was patency of the ductus arteriosus, which occurred alone in 4 cases and in combination in 5 cases. One of the cases with a patent ductus arteriosus also had coarctation of the aorta. In 4 hearts there were interventricular septal defects, and in 2 others the condition was complicated by pulmonary stenosis, dextroposition of the aorta and enlargement of the right ventricle, comprising the tetralogy of Fallot. A correct clinical diagnosis

had been made 7 times, in 4 adults and in 3 infants under 1 year of age. In 5 other persons, including an infant, the condition was suspected and the correct diagnosis had been entered on the record. In 3 patients congenital heart disease was diagnosed, but the anatomic defect was not noted. One of these had a cor biloculare. In another the condition was diagnosed wrong as to the congenital structural defect. In the remaining 25 patients, including 4 infants, congenital heart disease was entirely unsuspected.

Ash, Wolman and Bromer[1] pointed out that great difficulties attend the clinical identification of congenital heart defects during infancy. Widely different and entirely unrelated lesions may present similar murmurs or no murmurs and may give rise to identical roentgenologic configurations. The electrocardiograms showed no constant change except in the mirror picture dextrocardia. An enlarged thymus gland, a cluster of enlarged mediastinal lymph nodes, pulmonary atelectasis or pneumonia can confuse the interpretation of cardiac contour and position. They felt that by a correlation of the various findings a correct clinical diagnosis was often possible, although too much success should not be expected in the neonatal period, during which complicated abnormalities are frequent. They indicated that cyanosis is not a good criterion for differentiation of the various groups of lesions in infancy. It may be absent or delayed in the presence of lesions associated with venous-arterial shunt. Intermittent attacks may herald the presence of such a condition or may be merely transient phenomena associated with conditions in the "cyanose tardive" group. When transient attacks of cyanosis are produced by permanent shunt of unoxygenated blood into the peripheral circulation, careful scrutiny of the lips and the nail beds will often detect a slight tint of blueness between attacks. On the other hand, patients with "delayed cyanotic" lesions are customarily entirely free from cyanosis between attacks. Progressive cyanosis beginning in the first weeks of life should be interpreted as indicating a lesion with permanent venous-arterial shunt. Polycythemia may be an indicator of venous-arterial shunting of blood even when cyanosis is not apparent. Anemia resulting from infection or nutritional inadequacies may modify preëxistent polycythemia.

Heart murmurs in newborn infants were studied by Lyon, Rauh and Stirling.[24] They found murmurs in 147 infants of a series of 7637 newborn infants who were examined during the first week of life (an incidence of 1.9%). In considering etiologic factors, sex, the month of birth, the birth weight, and the occurrence of syphilis in the mother seemed to play no part in the incidence of the murmurs. Of this group of 147 infants, 92 were followed later in life; 4 had died and heart disease was found in the autopsies of 2 of these infants; 14 had persistent systolic murmurs which were considered to represent some form of congenital cardiac lesion. Of the 74 remaining, 71 were entirely well without any clinical evidence of heart disease and 3 had functional murmurs or extrasystoles. The writers believed that in the period of readjustment of circulation during the first few weeks of life, patencies of the foramen ovale and of the ductus arteriosus usually do not produce clinical cardiac murmurs and that many other congenital anomalies of the heart do not cause murmurs during the neonatal period.

An unusual case was reported by Ladd.[23] In a full term baby, delivered normally, it was noted that there was cyanosis when feeding was attempted and the infant choked and regurgitated. This difficulty was more marked with breast feeding than with artificial feeding. Diaphragmatic hernia was suspected and confirmed by Roentgen studies. At the age of 2 years the baby was hospitalized for operation. Above the opening in the diaphragm in the thoracic cavity there was found the stomach, the spleen and splenic flexure of the colon, half the transverse colon and about 10 cm. of the descending colon. On looking through the opening in the diaphragm the lung was seen collapsed and the heart next to it in the same cavity had no pericardial covering. No symptoms or signs betrayed the absence of the pericardium. Another unusual anomaly not included in the classification given above, was reported by Barlow.[3] This was a case of displacement of the heart with fissure of the sternum and no covering of pericardium or skin. This baby lived 60 hours.

In Ingham and Willius's[20] report of 5 cases of transposition of the great arterial trunks, in 1 instance partial transposition was present, both the aorta and the pulmonary artery arising from the right ventricle. In the other 4 cases complete transposition was present. In 4 cases the ductus arteriosus was patent and in 4 instances the foramen ovale was patent. An interventricular septal defect occurred in 2 cases. In 2 cases situs inversus was associated with the interventricular septal defect. A systolic murmur was heard in 4 of the 5 cases. The age of death varied from 18 days to 7 months.

Goodson[12] reported 2 unusual cases of coarctation of the aorta. In 1 case death occurred at the age of 16 years as the result of the rupture of an aortic aneurysm into a small bronchus. The other case was a girl of 19 years, in whom the condition was discovered during the course of a routine physical examination of basketball players. These cases exemplified the chief diagnostic criteria of the condition; brachial hypertension with femoral hypotension, visible collateral circulation, systolic thrill with diastolic shock at the base, absence of the aortic knob and faint erosion of the ribs as revealed by Roentgen ray. In the case confirmed at autopsy there were observed as well a bicuspid aortic valve and an anomalous right coronary artery. The other case illustrated the fact that this condition is not incompatible with life and with apparently good health.

Semans and Taussig[33] recorded the presence of an enormous saccular dilatation of the left auricle in a 5-year-old child. The condition was believed to have been due to a congenital abnormality either in the blood supply of the affected area or in the auricular myocardium. The thickening of the mitral valve and shortening of the chordæ tendineæ are believed to have been associated with the congenital malformation of the heart. The fact that the enormous saccular dilatation of the left auricle extended to the left and that it occurred in conjunction with incomplete dextrocardia offered strong evidence that both conditions represented congenital anomalies.

Emenheiser[10] reported 10 cases of congenital dextrocardia. In this group there were 8 females and 2 males, all of whom were white persons. The usual mirror type of dextrocardia, with transposition of the abdom-

inal viscera, was found in 8 cases. Congenital dextrocardia with the thoracic aorta descending to the left side of the vertebral column without the transposition of abdominal viscera and unaccompanied by other serious anomalies was seen in 1 patient. Another showed the thoracic aorta descending on the right side of the vertebral column without the transposition of abdominal viscera, but accompanied by other serious anomalies. Electrocardiograms made in cases of congenital dextrocardia with transposition of the abdominal viscera showed the pathognomonic sign of inversion of all waves in Lead I and transposition of Leads II and III. The electrocardiograms made in the cases of congenital dextrocardia without transposition of abdominal viscera did not show these pathognomonic signs.

Taussig[35] gave the clinical and pathologic findings in congenital malformations of the heart due to defective development of the right ventricle and associated with tricuspid atresia or hypoplasia. The central feature in this congenital malformation is the diminutive size of the right ventricle. The associated malformations develop because the right ventricle does not function and as a result neither the tricuspid valve or the pulmonary valve can function so that both are either artresic or markedly hypoplastic. In addition, the only way for the blood to escape from the right auricle is through some defect in the interauricular septum. The extent of this defect determines whether the heart functions as a biloculate or triloculate organ. Clinically, the malformation is associated with persistent cyanosis and no murmurs. The diagnosis is established through the recognition of the very small size of the right ventricle. This gives a peculiar outline in the roentgenographic shadow. In the antero-posterior view, because of the absence of the pulmonary conus, the upper contour of the cardiac shadow immediately to the left of the sternum has a concave instead of a convex outline. In the left anterior oblique position the small size of the right ventricle is indicated by the absence of a cardiac shadow anterior to that of the aorta. These observations were substantiated by the electrocardiogram which shows a deviation of the axis to the left. The differentiation between functionally biloculate and triloculate hearts depends on the size of the interauricular septal defect. If there is a free communication between the two auricles or if the heart is functionally biloculate, physical examination yields no additional positive findings. When the interauricular septum is well formed it causes obstruction to the outflow of the blood from the right auricle. Under these circumstances the auricular pulsation is transmitted to the liver and is readily palpable at its margin. It is this pulsation at the edge of the liver, occurring in conjunction with the diminutive right ventricle, which distinguishes a functionally triloculate heart from one that is functionally biloculate.

Kugel[22] pointed out that only in recent years has it been demonstrated that in many cases so-called "idiopathic hypertrophy" of the heart was in reality associated with congenital malformations as well as rheumatic fever, glycogen-storage disease, myocardial degeneration of the heart and fibrosis. Cases of dilatation and hypertrophy of the heart associated with myocardial degeneration and fibrosis, constituted the majority of the cases. In most instances the causes and nature of

the enlargement of the heart in an infant could be determined. The chief features were enlargement of the heart without known cause, an afebrile course, the sudden onset of symptoms, dyspnea and cyanosis and the lack of signs or history suggestive of congenital heart disease, rheumatic fever, diphtheria, infections and anemia or metabolic disturbances. Some examples of this condition appear to be examples of von Gierke's glycogen-storage disease localized in the heart (Finkelstein[11]).

Radiologically, the diagnosis of congenital malpositions may be indicated by tracheal displacement in the inspiratory phase, according to Pendergrass and Allen.[31] They found this in 9 cases of congenital heart disease which at autopsy showed complete transposition of great vessels in 2 cases, partial transposition of great vessels in 2 cases, dextroposition of the aorta in 1 case, complete transposition of heart and great vessels in 1 case and multiple intrinsic defects in the heart in 2 cases. In 150 normal infants tracheal displacement did not occur in the inspiratory phase. They pointed out that in the normal at the thoracic inlet the trachea occupies practically a midline position in the postero-anterior view during the peak of the inspiratory phase of the respiration. From the thoracic inlet to the bifurcation of the trachea there is a slight deviation to the right. This is not true in the expiratory phase, at the height of which there is a marked buckling and deviation to the right. In the lateral view at the peak of the inspiratory phase the trachea occupies almost a straight course in its cervical and thoracic portions. In the expiratory phase there is some buckling of the trachea at the thoracic inlet associated with a moderate diminution in the caliber of the lumen.

Not only is congenital heart disease the result of malformations of the chambers and great vessels but there are reports of congenital heart disease due to other factors. Among these conditions is congenital heart block, according to Wallgren and Winblad,[38] first reported by Van der Heuvel in 1908. The most informative reports have been those of Yater and his collaborators in the United States, and Nielsen in Scandinavia. In order to make a definite diagnosis of congenital heart block it should be established by graphic records in a relatively young person without other apparent cause. Bradycardia must have been demonstrated at an early age. There must be no history of an infection that might have been responsible for the heart block. The total number of such cases in the literature is 77, which includes 2 cases reported by these authors. These showed fetal bradycardia. In 1 case the dissociation between the auricle and the ventricle was confirmed by fluoroscopic examination and in the other by electrocardiogram. In the first case at autopsy, although the heart was grossly normal, the bundle of His was interrupted for a short distance from the atrioventricular node by the fibrous tissue of the annulus fibrosus. In the other case, the ventricular septum was patent and the bundle of His was found only as a degenerated remnant, which lay in a strand of fibrous tissue and was separated both from the auricular muscle and from the normally developed portions of the ventricular conduction system. In the first patient the anomaly was regarded as of independent origin, but in the second it was evidently correlated with failure of formation of the interventricular septum.

Heubner[18] reported a case of congenital heart block. It was noted during delivery that the rate of the fetal heart sounds was extremely slow, not rising over 80 per minute even after the fetal head had entered the true pelvis. A healthy baby was born spontaneously. The heart rate was very slow, but no pathologic phenomena were noted on auscultation. The electrocardiogram showed bradycardia of 60 beats per minute. The auricular waves were not directly related to the ventricular complex and the *T* waves were diphasic in Leads II and III. In all probability there was a 2 to 1 block during and after birth. In other cases of congenital heart block reported in the literature the patients died a short time after birth and the autopsies showed severe defects. In this case there probably was a mild disorder which cleared up during the early months of the baby's development.

Harris[16] has reminded us that the treatment of a case of congenital heart disease is limited in its scope by the very nature of the condition. The lesions are present fully developed from birth. Treatment is confined, therefore, to adapting a damaged individual to a life which shall be as nearly normal as possible. In order to do this he recommended that it is necessary to determine to what degree the function of the heart has been damaged. In doing this the patients were classed into three groups. The first group consists of those who had such severe damage that they could not survive by more than a few days or weeks. The second group was made of those whose lesions, though severe, were compatible with a life of limited activity and stress. The third group were those who had congenital heart lesions, which did not interfere with cardiac efficiency. The second group was the one which deserved most consideration in the question of treatment. The management of these cases may be epitomized under three headings: the regulation of exercise, the anticipation and prevention of intercurrent disease, and education for a suitable vocation.

More active treatment was recommended in patent ductus arteriosus by Hubbard, Emerson and Green.[19] They emphasized the need of determining whether or not there was an arteriovenous shunt large enough to impair the normal cardiac function and the peripheral circulation. The evidence to be looked for was a delay in the growth and development of the child, any signs or symptoms of cardiac insufficiency and, more specifically, the signs of free aortic regurgitation, congestion or pulsation of the pulmonary vessels at the hilus of the lung as seen by Roentgen ray. These signs should be considered as danger signals and once they have been established surgical intervention should be considered in the hope of abolishing the excessive load on the heart, restoring normal circulation, allowing normal growth and eliminating the danger of heart failure. In reporting 4 cases in which patent ductus arteriosus was obliterated without mortality, Gross, Emerson and Green[13] stated that a persistently patent ductus arteriosus, after the first few years of life, was an important cardiovascular abnormality which may lead to serious and even fatal complications in adolescence or in adult life. The greatest of the impending dangers was subacute bacterial endocarditis. The next most important hazard was cardiac decompensation, which results from overwork of the heart produced by the arteriovenous communication. While most patients with patent

ductus arteriosus showed little or no disability during childhood, they are laying the foundations for later trouble by building atheromatous plaques in the pulmonary artery which may be later the site of bacterial vegetations, or they are so overexercising the heart that decompensation may occur one or two decades later. These authors claimed that, if operative ligation of the patent ductus arteriosus can be performed early in life, the degenerative changes in the pulmonary artery should be arrested and the danger of subsequent bacterial endocarditis should be decreased. At the same time ligation of the arteriovenous shunt greatly reduced the work of the heart and cardiac reserve should be increased.

In a number of studies on San Francisco school children Sampson, Christie and Geiger[32] found the percentage of children with congenital heart disease to be extremely high, and from this they concluded that the incidence of rheumatic heart disease was correspondingly low. In 13,338 school children 197 had heart disease. In this group the incidence of organic heart disease was 3.7 per 1000 of population, of which 2.2 had rheumatic heart disease and 1.4 congenital heart disease. This is interesting in passing but it is difficult to evaluate the relative hazard to the child of congenital heart disease and acquired heart disease unless more comprehensive statistics are available. This is not possible in a survey of school children but must include reports on babies who are stillborn, those that die in the neonatal period and even during the first years of childhood. This is necessary to get a proper conception of the rôle that congenital lesions play as usually only the less severe lesions allow survival up to the school age.

Turning to acquired heart disease among children, while rheumatic fever is its chief cause, the other infectious disease of childhood may result in similar residual damage to the heart. In a follow-up study of 1000 patients with rheumatic fever treated at the House of the Good Samaritan in Boston, Jones[21] found that at the end of 10 years 242 (24.2%) were dead, 310 were potential subjects of rheumatic heart disease and 427 had rheumatic heart disease. Of the 427 living patients with rheumatic heart disease there was no limitation of activity in 287, the limitation was moderate in 119 and in 21 there was a serious physical handicap. He stressed the importance of early recognition of the condition and the prevention of respiratory infections in these individuals.

Stroud, Goldsmith, Polk and Thorp,[34] in a study of 458 children, found that the average age of the primary manifestation of rheumatic fever was 7.3 years. Of the 307 children concerning whom information was available, 125 were dead or totally disabled and 182 were working or able to work or to go to school. Of a total of 428 primary manifestations and reactivations concerning which positive information was available, 61% occurred during the months of December and May, with a peak of 15.2% during March. Because of these figures they stressed the necessity of increased prophylactic care during these months in susceptible children between the ages of 6 and 10 years, as these are the years during which primary manifestations and reactivations are most apt to occur. In this group by far the greatest number of patients were Italian, Hebrew, American and Irish, in the order named. It was seen also that there was a familial incidence at least as high as

that in tuberculosis. As far as this study was concerned, measures to protect children with rheumatic heart disease from the common cold and other infections of the respiratory tract offered the most practical form of prophylactic treatment.

The natural history of rheumatic fever in the first three decades of life was the subject of a report by Wilson[40] of a 20-year period of observation on the course of the disease in 337 subjects. Of these, 225 had lived to ages of from 16 to 30 years and 112 had died of the disease. The onset from childhood was characterized by many varied manifestations of activity and by a varied number of years of freedom from recurrence or by continuous years of manifestation of active infection. After puberty, at about the age of 16 years, 66% of the subjects were free from recurrence of symptoms compared with the 13% before this age. The disease seemed to be self-limited, as death occurred in most instances of active carditis. The first attack of carditis was sometimes fatal, but the majority survived the first and even several subsequent attacks. The average at which death occurred was 12.6 years and the greatest incidence of death was in the group from 12 to 16 years. The type of rheumatic manifestation, exclusive of active carditis, did not appear to be of prognostic significance. The incidence of carditis was comparable whether the patient had pains in the joints alone, or chorea, or polyarthritis with or without pains in the joints. All of the subjects presented evidence of cardiac involvement, although in only 39% were the symptoms of carditis apparent clinically and in these patients the amount of cardiac damage was greater and the mortality higher. During the course of the disease physical signs of valvular involvement disappeared or were inconstant or uncharacteristic and led to considerable error as to the condition of the heart. The presence of considerable cardiac enlargement that could be demonstrated only by roentgenographic methods was an indication of the difficulty in establishing a diagnosis of cardiac hypertrophy by physical examination alone. Among those that survived, the majority were able to carry on their work without circulatory symptoms, and this was true especially of those past the age of puberty, and the author strongly emphasized the possibility that the idea that most rheumatic patients die in the third and fourth decades, was unfounded.

Cushing[7] indicated that heart disease was the most important cause of death now registered, as it accounted for 10% of all deaths and exceeded all other causes of death and disease, even including tuberculosis. In the careful routine examination of school children, from 2 to 5% show evidence of organic heart disease and of these 90% are due to rheumatic fever. Thus rheumatic heart disease is the outstanding threat against child health, and the seriousness of this is exaggerated by lack of knowledge. Stressing the needs in this direction, Jones[20] presented a plea for the early recognition of rheumatic fever which he considered the common cause of heart disease in children. Not only is it a threat against life but it often is the result of heart lesions that causes the individual to be a cardiac cripple. Marsh[27] also emphasized the same points and stated that the children with heart disease are just as truly crippled as those with bone deformities or paralyses.

Ball[2] pointed out that the major clinical manifestations of rheumatic disease are arthritis, carditis and chorea. He considered carditis as the most important as it most often leads to permanent damage. However, there is often some relationship of all three. Parrish, Taran and Starr[30] studied the incidence of cardiac disease in a group of children who had had one or more attacks of Sydenham chorea uncomplicated by any rheumatic manifestation and made a comparison of this incidence with the incidence of cardiac disease in a group of children presenting histories of chorea plus other manifestations of rheumatism. In this study 78 children had had one or more attacks of chorea without any rheumatic symptoms, while 34 had had both chorea and rheumatic symptoms. Of the entire group 59.8% had definite cardiac involvement. The incidence of cardiac involvement in the purely choreic group was 52.5% and in the mixed group 76.4%. While their figures do not agree with others previously published in one report, they do agree with the figures of another report and consequently the authors concluded that until the causes of rheumatism and chorea are better known, it would be advisable to assume that chorea is one of the rheumatic manifestations.

This opinion was held also by McCulloch.[25] In his paper he stated that it had been implied throughout his discussion that the chorea minor of Sydenham was a rheumatic manifestation and that such was the case was believed in his department. For this reason he suggested that the term encephalitis rheumatica was proper and more descriptive. It should serve to distinguish such cases from all others with a more obvious etiology or from those with idiopathic chorea of unknown etiology. Since the attack of chorea may be the first manifestation of the rheumatic state in the child, all cases must be watched for further fever. On the other hand, the rheumatic state may precede the chorea and there may be some overlapping in the diagnosis of all children. It was also suggested that the encephalitis of rheumatic fever was similar in its anatomic process to the arthritis, the acute pericarditis and myocardial changes of an exudative attack of rheumatic fever.

Diphtheria is regarded as an important factor in the development of acquired heart disease in childhood. Burkhardt, Eggleston and Smith[6] made serial electrocardiograms of 140 patients showing evidence of toxic diphtheria. Changes of contour were shown in 28 of these. In 23 cases the *T* wave changes occurred between the fifth and the thirteenth day of illness. The majority of changes occurred between the eighth and the fifteenth days of illness. In 17 cases conduction changes were shown between the fifth and thirteenth day of illness. In all of these cases atrioventricular dissociation developed and this complication invariably proved fatal. Fourteen patients died of toxic diphtheria. Diphtheria antitoxin in large doses was given to 7 of these on or before the fourth day of illness, so that it is evident that early administration of antitoxin did not give an advantageous result in this group of patients. Peripheral nerve palsies developed in 65% of the patients that showed electrocardiographic changes, but there was no apparent causal relationship to the cardiac phenomena. The essential histologic changes in the myocardium resulting from toxic

diphtheria are edema, congestion, cellular infiltration, degenerative changes in the muscle fibers and ultimately fibrosis. The electrocardiographic findings were recommended as an important guide to treatment. Where the serial electrocardiograms showed abnormalities it was necessary to maintain complete inactivity until there was a return to the normal.

As regards the myocardial changes, Oheim[29] studied 50 fatal cases of diphtheria in which there were no complicating infections or other complicating conditions. The successive changes were interstitial edema, myolosis, waxy degeneration, calcification, fatty degeneration, proliferation of fixed cells in the spaces arising from muscle cell degeneration, and leukocytic and lymphocytic infiltrations. Interstitial edema and initial myolosis appeared first on the second to the fourth day of the disease, while the other changes reached the height of intensity from the seventh to the thirteenth day. Repair by connective tissue proliferation had commenced by the tenth day. The most severe lesions were observed in the subendocardial and ring muscle layers of the myocardium, especially that of the right ventricle.

Scarlet fever as well as diphtheria comprised the study of Berger and Olloz.[4] They made electrocardiographic observations on 66 cases of scarlet fever and 31 cases of diphtheria. In 52 of these cases there were no clinical or electrocardiographic alterations, while in 14 cases there was evidence of cardiac affection. In their 31 cases of diphtheria 26 were normal both clinically and electrocardiographically.

Hartwell[17] stated that while cases of meningococcic septicemia are common in reports in the literature, those in which the accompanying endocarditis and myocarditis have been proved definitely were rare. He found only 17 case reports of endocarditis and 12 of myocarditis caused by the meningococcus. He reported a case that was proved at postmortem examination. In summing up all available material on the subject he stated that the patients usually died. The lesions were usually mitral in location and the myocardial lesions were probably more common than is recognized at the present time. Metastatic lesions were not infrequent, although there was difficulty in recognizing them clinically. Usually the diagnosis of the meningococcic septicemia was made by blood culture during the clinical course of the disease, but the endocarditis was frequently overlooked.

Thompson[37] reported the case of a 4-year-old girl who had whooping cough complicated by bronchopneumonia and an unusual degree of congestive heart failure, proceeding to general anasarca. There was no evidence of a preëxisting heart disease although there was a history of a faucial diphtheria some 8 months before. The author pointed out that some investigators maintain that apart from cardiac dilatation during the paroxysmal stage some attacks of pertussis have left permanent damage and even valvular disease. There are others who agree that a temporary mechanical strain may occur, affecting more particularly the right side of the heart, but heretofore there has been found no permanent damage either of the myocardium or of the endocardium.

While other infectious disease of childhood may cause cardiac lesions that are permanent, that carditis may occur with scurvy and other

nutritional disorders is not so generally known. Taylor[36] pointed out that Erdheim showed in 1918 that scurvy may be associated with cardiac lesions. Taylor's study was based on experiments with guinea pigs. It was found that guinea pigs suffering from scurvy showed cardiac valvulitis, myocarditis and occasionally pericarditis, often associated with Gram-positive organisms even when none had been injected. The lesions were commonest in the mitral valve, the auriculoventricular junction, the perivascular areas in the myocardium and the papillary muscles. Intradermal injections of hemolytic streptococci did not increase the incidence or severity of the lesions but increased the incidence with which the organisms were found in the heart. When infected guinea pigs were kept in a state of subacute scurvy for a considerable time, they acquired congestion of the lungs and liver. Once the lesions of the heart had developed, curing the scurvy did not remove the lesions, although it did prevent the development of congestive heart failure.

Along somewhat similar lines Waring[39] discussed nutritional heart disease although his observations were made on children instead of on experimental animals. It would seem that avitaminoses can be the cause of cardiac damage. In his cases he made the diagnosis of nutritional heart disease on the following findings: cardiac enlargement shown by percussion and by Roentgen examination and usually not accompanied by murmur; negative results of urinalyses; absence or sluggishness of reflexes; a history of a deficient diet, and more or less rapid response to rest and sufficient food. His 13 patients were children whose ages varied from 14 to 48 months and averaged 25 months. Only 1 was white. The cause of the cardiac enlargement did not appear in these cases. It was not known whether the deficiency of vitamin B_1, deficiency of protein or general dietetic deficiency was the fundamental cause. These cases did not always manifest rapid reduction in size. Scurvy was not evident in these cases and rickets was not apparently active. All of the patients improved on adequate diets fortified with materials rich in vitamin B_1 such as brewer's yeast, wheat germ sugar and extract of rice polishings. In addition to these cases of cardiac disorder, 34 cases of nutritional edema without evident cardiac disease were observed. None of these had clinical cardiac enlargement nor Roentgen evidence of cardiac hypertrophy. In general, the histories and clinical conditions were similar to those of the children having cardiac lesions, and the age period incidences were parallel. It seemed probable that there were some cardiac changes that were not demonstrable. Electrocardiographic examination should be made as changes have been observed by this method in epidemic dropsy. These alterations included sinus tachycardia, sinus arrhythmia, short P–R interval, occasional auricular fibrillation, coronary T wave and other abnormalities of the T wave that suggested myocardial damage.

Hafkesbring, Drawe and Ashman[14] studied the electrocardiograms of 100 normal children in order to establish the normal variations. They found that the duration of the P wave averaged 0.062 second. The upper limit was 0.09 second. The height of the P wave in Lead I was slightly higher than the average for the adult and the upper limit should be placed at about 1.5 mm. A P_2 measuring over 2.5 should be con-

sidered above normal. A diphasic or slightly inverted P_3 was occasionally found in the electrocardiogram of a normal child. Slight and questionable notching of the P wave was occasionally seen, but no definite or conspicuous notching of the P wave was found in the electrocardiogram of a normal child. The average P–R in this series was 0.132 second, and there was no significant difference according to sex. The P–R interval was found to show a tendency to increase with increasing age and to decrease with increasing heart rate. The average duration of the QRS phase was 0.065 second. The QRS showed an increase in duration with the increase in age. QRS of low voltage was found in only 1 of 100 electrocardiograms of normal children. There was no great difference in the heights of the R wave for children and those for the R wave of adults. The electrical axis in all but 3 cases ranged between 20 and 104 degrees and extended from a slight left axis deviation to a slight right axis deviation. Slight shifting of the RS–T segment, especially upward, was occasionally seen. The T waves consistently averaged higher for the boys than for the girls, even in different age groups. T_3 was frequently inverted. Low T waves were found in only 1 case and this might not have been a perfectly normal individual. Premature beats were rare.

Studying children with rheumatic heart disease and congenital heart disease Drawe, Hafkesbring and Ashman[8] in the rheumatic group found that the principal abnormality of the P wave was definite and conspicuous notching, widening and slight increase in height. The P–R interval was definitely prolonged in a large percentage of cases of rheumatic heart disease. The abnormalities of the QRS complex were relatively slight, consisting of a small increase in duration and occasional notching or slurring of the individual waves. Only a slight tendency to right axis deviation was shown in the electrocardiograms of children with mitral stenosis and insufficiency. This was probably due to the fact that in most of these cases the condition was not far advanced. The children with aortic regurgitation showed a definite tendency to left axis deviation. The incidence of shifts of the RS–T segment was increased, but not so markedly as others have reported. Abnormalities of the T waves were found in 10% of the cases. These abnormalities consisted of low T waves in all leads, diphasic T waves in Lead I, and low, rounded, notched and inverted T waves in Lead II. The QT interval was often definitely prolonged. As with normal children the incidence of premature beats was low. Some children with rheumatic heart disease had normal electrocardiograms. In the children with congenital heart disease the outstanding abnormalities of the P wave were increases in the width and in the height, and these were found in the electrocardiograms of children with pulmonary stenosis and the tetralogy of Fallot and to a lesser degree in those of children with intraventricular septal defect. The notching of the P wave was not beyond normal limits. The P–R interval was approximately the same as it was in the electrocardiograms of the normal group. The average duration of the QRS was longer than in normal children. Notching and slurring of the QRS segment occurred frequently in children with pulmonary stenosis, occasionally in those with intraventric-

ular septal defect, and rarely in cases of patent ductus arteriosus. All the electrocardiograms of children with pulmonary stenosis showed extreme, conspicuous or definite right axis deviation. The T waves averaged considerably higher than the normal group, and the T waves of the males averaged considerably higher than those of the females. Abnormalities of the T wave were occasionally found, consisting of inversions of T_2 and deep inversions of T_3. In a few instances the QT was slightly prolonged.

Another interesting contribution concerning electrocardiograms in children was the study of Lead IV in normal children and in ambulatory cases of cardiac disease by Messeloff and Pomerantz.[28] They found that the electrocardiograms of children were characterized by a marked variability in the form and the direction of its several components. Upright, diphasic and iso-electric T_4 waves were normal findings in the tracings of children. In this series of tracings for ambulatory children with heart disease Lead IV supplied no information which was not secured from the three standard leads. For this reason it was concluded that there was no definite reason for the routine use of Lead IV for ambulatory children with heart disease.

As a concluding reference in this review it is in keeping with its importance to mention the observations of Hamburger.[15] He emphasized that cardiac capacity for work is more important than any condition that is disclosed by physical, Roentgen or electrocardiographic examination. With patients in bed without fever or involvement of joints the activity used in testing can be rising to the sitting position several times. For ambulatory patients it can be squatting or stair climbing. The physician can accompany and observe the child on a walk either over a level surface or uphill. Acceleration of respiration and dyspnea are more important points than the acceleration of heart action, which may be affected by psychic influences. Respirations should be observed without the child's knowledge.

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The Nature of the Permanent Diabetes Produced by Anterior Pituitary Extract. F. C. Dohan, C. A. Fish, and F. D. W. Lukens (George S. Cox Medical Research Institute, University of Pennsylvania). Ten dogs have been made permanently diabetic by the injection of anterior pituitary extract (Young). The results of studies on these animals support the conclusions previously reached that, after it is established, the diabetes is comparable to pancreatic diabetes. The degree of the diabetes has varied but in 3 severely diabetic dogs the secretion of glucose and nitrogen during fasting is similar to that of totally depancreatized animals. The response to insulin, respiratory metabolism, and the consistent occurrence of marked atrophy of the islands confirm the early conception of the pancreatic nature of this condition. Our studies also show that after the termination of injections of pituitary extract the diabetes tends to become gradually more severe. This progress is retarded by insulin treatment, although no recovery of the atrophic islands has been noted.

Respiratory Metabolism of the Porpoise. Laurence Irving, P. F. Scholander, and S. W. Grinnell (Edward Martin Biological Laboratory, Swarthmore). As a species of small-toothed whale the porpoise, *Tursiops truncatus*, encounters the respiratory difficulties common to all whales. We have examined in 9 porpoises the characteristics of breathing and internal respiration in order to see how the respiration of whales proceeds and to gain light on how mammalian respiration operates when breathing is infrequent. During the course of our observations the porpoises usually breathed from 2 to 4 times a minute and during each respiratory pause the heart gradually slowed to about 40 beats per minute and then increased to about 80 a few seconds after taking a breath. Heart records were taken with the electrocardiograph.

During a 2-minute dive in the open sea the heart slowed to about 30 and remained retarded during active swimming under water. It appears likely that the bradycardia is associated with the elective control of circulation which is known to exist in several mammals during apnea. For comparison with the cardiac response in man it was found that the heart rate of a practiced and able diver at Silver Springs, Florida, slowed while he stood quietly under water to about 30. Even while swimming vigorously under water the bradycardia persisted. Measurements of the respiratory metabolism of porpoises weighing about 180 kg. by means of a large Krogh spirometer showed that each inspiration took in from 6 to 10 liters and about 10% of that volume of oxygen was utilized. The resting oxygen consumption was about 1 liter per minute. At each expiration the lungs were almost completely emptied, the residual air being determined at about 20% of the inspired air. The alveolar CO_2 was between 7 and 10%. It appears that porpoises are like several other diving animals which are relatively insensitive to CO_2. During or after a forced dive of 2 or 3 minutes' duration it was remarkable that the alkali reserve of the blood changed very little, and scarcely any increment of lactic acid appeared either in blood or muscles. Although fatal asphyxia could be caused in 3 minutes the absence of the acid as a sign of anaerobiosis was surprising. These observations point out the mechanics and dimensions of the respiratory system in the porpoise. They also show how certain typical mammalian respiratory mechanisms operate under the peculiar conditions in which an aquatic mammal lives.

How Do We Perceive the Pulse? F. H. Lewy and B. Lewy (by invitation) (Department of Neurosurgery, University of Pennsylvania). The arterial pulse can be felt by palpation by only a few areas of the body surface, namely the volar surfaces of the fingers and hand, the plantar surfaces of the toes and the heel, the lips, and the tongue when passively pressed against the artery. The acuity of perception of pulsation follows Weber's scala for spatial discrimination. The skin areas sensitive to pulsation are invested with the greatest number of touch points per square centimeter, and their sensory nerves have the greatest velocity of conduction. Thus, the skin areas sensitive to the pulse beat possess the two main prerequisites of stereognosis. "Feeling the pulse" is a stereognostic function because, in addition to counting the frequency of the pulse beats, the examiner is concerned with appreciation of the profile of the pulse wave, the recognition of its qualities, and with its classification.

Excretion of Sodium Pregnandiol Glucuronidate in Urine of Normal Human Pregnancy. C. Bachman, D. Leekley, and H. Hirschmann (Gynecean Institute, University of Pennsylvania). The method of Venning and Browne for the recovery of pregnandiol glucuronidate from urine was employed for a study of the excretion of this compound during normal gestation in 6 healthy young women. The results fully confirmed the

earlier findings of Venning, Henry and Browne concerning the quantities excreted at various periods of normal pregnancy. In addition, excretion during gestation in our cases was marked by slight cyclic monthly remissions, and by a pre-labor fall. Additional data, obtained from 4 cases of multiple gestation, suggested that the quantities of pregnandiol glucuronidate excreted in such cases did not differ significantly from those excreted at corresponding periods of single-fetus gestations.

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